Title Page

Protocol Title:		Effect of Erenumab-aooe on Disability and Work Productivity in Employed Subjects With Episodic Migraine Who Have Previously Failed 1 or More Migraine Preventive Treatments
Short Protocol Title:		Effect of Erenumab-aooe on Disability and Work Productivity in Employed Subjects With Episodic Migraine
Protocol Number:		20180060
Investigational Product:		Erenumab-aooe (AMG 334)
Trade Name:		AIMOVIG®
Sponsor	**Name of Sponsor:**	Amgen Inc.
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EudraCT Number:		Not applicable
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Version/Date:		**Data Element Standards Version** Version 6.1

This protocol was developed, reviewed, and approved in accordance with Amgen's standard operating procedures.

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Investigator's Agreement:

I have read the attached protocol entitled, Effect of Erenumab-aooe on Disability and Work Productivity in Employed Subjects With Episodic Migraine Who Have Previously Failed 1 or More Migraine Preventive Treatments dated **31 August 2020**, and agree to abide by all provisions set forth therein.

I agree to comply with the International Council for Harmonisation (ICH) Tripartite Guideline on Good Clinical Practice (GCP), Declaration of Helsinki, and applicable national or regional regulations/guidelines.

I agree to ensure that Financial Disclosure Statements will be completed by: me (including, if applicable, my spouse or legal partner and dependent children) and my subinvestigators (including, if applicable, their spouses or legal partners and dependent children) at the start of the study and for up to 1 year after the study is completed, if there are changes that affect my financial disclosure status.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Amgen Inc.

_____
Signature

_____ _____
Name of Investigator Date (DD Month YYYY)

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1. Protocol Synopsis

Protocol Title: Effect of Erenumab-aooe on Disability and Work Productivity in Employed Subjects With Episodic Migraine Who Have Previously Failed 1 or More Migraine Preventive Treatments

Short Protocol Title: Effect of Erenumab-aooe on Disability and Work Productivity in Employed Subjects With Episodic Migraine

Study Phase: 4

Indication: Preventive treatment of migraine in adults

Rationale:

The presence of various comorbidities in migraine patients, whether associated or migraine-induced, has been established by numerous studies. These comorbidities contribute to migraine-related disability, impacting work and overall function (Lipton et al, 2013; Stewart et al, 2008). The American Migraine Prevalence and Prevention (AMPP) study of patients with episodic migraine (EM) evaluated several domains of headache-related disability such as work, depression, and anxiety, to name a few, that are frequently affected by migraine. Other studies, though smaller in scale, have demonstrated the impact of migraine on quality and quantity of sleep (Barbanti et al, 2007; Kelman and Rains, 2005).

Closer analyses of impact of migraine on work have not only revealed absence from work, but also reduction in performance also known as presenteeism (Stewart et al, 2008). Relevant components of decreased presenteeism include impaired concentration and feeling of fatigue.

In phase 2 and 3 clinical trials, erenumab-aooe (referred to as erenumab herein) has demonstrated a reduction in monthly migraine days (MMD) as well as migraine-related disability (Dodick et al, 2018; Tepper et al, 2017; Goadsby et al, 2017b). **Separately,** improvement in MMD and migraine-related disability have been associated with improvement in work productivity (Dodick et al, 2016; Lipton et al, 2013).
Study 20180060 is being conducted to confirm the effect of erenumab on migraine-related disability (inclusive of aforementioned comorbidities) and work productivity.

Objective(s)/Endpoint(s)

Objectives	Endpoints
Primary	
• To evaluate the effect of erenumab compared to placebo on disability in employed subjects with episodic migraine (EM) who have previously failed 1 or more migraine preventive treatments	• Sum of monthly changes from baseline in modified Migraine Disability Assessment (MIDAS) total score over the 6-month double-blind treatment period (DBTP)
Primary Estimand	
The primary estimand for the primary objective on migraine-related disability consists of: • The target population, which includes employed subjects with EM who have previously failed 1 or more migraine preventive treatments • The endpoint, which is the sum of monthly changes from baseline in modified MIDAS total score over the 6-month DBTP • The intercurrent event is adherence to treatment. The treatment effect of interest will be assessed for all randomized subjects enrolled from traditional sites who receive at least 1 dose of investigational product (IP) and have a baseline value and at least 1 post-baseline value of modified MIDAS total score, regardless of adherence to treatment • The summary measure, which is the difference in means of the endpoint between the erenumab group and the placebo group The primary estimand is the difference in means between erenumab and placebo of the sum of monthly changes from baseline in modified MIDAS total score over the 6-month DBTP in employed subjects with EM who have previously failed 1 or more migraine preventive treatments and who are randomized, receive at least 1 dose of IP, and have a baseline value and at least 1 post-baseline value of modified MIDAS total score, regardless of adherence to treatment.	
Secondary	
• To evaluate the effect of erenumab compared to placebo on monthly migraine days (MMD) in employed subjects with EM who have previously failed 1 or more migraine preventive treatments	• Change from baseline in mean MMD over months 4, 5, and 6 of the 6-month DBTP
The estimand for the secondary objective on MMD consists of: • The target population, which includes employed subjects with EM who have previously failed 1 or more migraine preventive treatments • The endpoint, which is the change from baseline in mean MMD over months 4, 5, and 6 of the 6-month DBTP • The intercurrent event is adherence to treatment. The treatment effect of interest will be assessed for all randomized subjects enrolled from traditional sites who receive at least 1 dose of IP and have a baseline value and at least 1 post-baseline value of MMD, regardless of adherence to treatment. • The summary measure, which is the difference between the mean of the endpoint for the erenumab group and the placebo group	

Objectives	Endpoints
Secondary (Continued)	
The estimand is the difference in means between erenumab and placebo of the change from baseline in mean MMD over months 4, 5, and 6 of the 6-month DBTP in employed subjects with EM who have previously failed 1 or more migraine preventive treatments and who are randomized, receive at least 1 dose of IP, and have a baseline value and at least 1 post-baseline value of MMD, regardless of adherence to treatment.	
• To evaluate the effect of erenumab compared to placebo on work impairment in employed subjects with EM who have previously failed 1 or more migraine preventive treatments	• Change from baseline in mean monthly percent work impairment over months 4, 5, and 6 of the 6-month DBTP, as measured by the Work Productivity and Activity Impairment Questionnaire (WPAI): Migraine V2.0 (WPAI questions 2, 4, and 5) Note: the monthly percent work impairment equals to the arithmetic mean of the observed weekly percent work impairment over the monthly interval.
The estimand for the secondary objective on work impairment consists of: • The target population, which includes employed subjects with EM who have previously failed 1 or more migraine preventive treatments • The endpoint, which is the change from baseline in mean monthly percent work impairment over months 4, 5, and 6 of the 6-month DBTP • The intercurrent event is adherence to treatment. The treatment effect of interest will be assessed for all randomized subjects enrolled from traditional sites who receive at least 1 dose of IP and have a baseline value and at least 1 post-baseline value of monthly percent work impairment, regardless of adherence to treatment. • The summary measure, which is the difference in means of the endpoint between the erenumab group and the placebo group The estimand is the difference in means between erenumab and placebo of the change from baseline in mean monthly percent work impairment over months 4, 5, and 6 of the 6-month DBTP in employed subjects with EM who have previously failed 1 or more migraine preventive treatments and who are randomized, receive at least 1 dose of IP, and have a baseline value and at least 1 post-baseline value of monthly percent work impairment, regardless of adherence to treatment.	
• To evaluate the effect of erenumab compared to placebo on physical function, usual activities, and social function in employed subjects with EM who have previously failed 1 or more migraine preventive treatments	• Change from baseline in mean physical function domain score over months 4, 5, and 6 of the 6-month DBTP, as measured by Migraine Functional Impact Questionnaire (MFIQ) • Change from baseline in mean usual activities domain score over months 4, 5, and 6 of the 6-month DBTP, as measured by MFIQ • Change from baseline in mean social function domain score over months 4, 5, and 6 of the 6-month DBTP, as measured by MFIQ

Objectives	Endpoints
Secondary (Continued)	
The estimand for the secondary objective on function (physical, usual activities, and social) consists of: • The target population, which includes employed subjects with EM who have previously failed 1 or more migraine preventive treatments • The endpoints include: 1) the change from baseline in mean physical function domain score over months 4, 5, and 6 of the 6-month DBTP, as measured by MFIQ 2) the change from baseline in mean usual activities domain score over months 4, 5, and 6 of the 6-month DBTP, as measured by MFIQ 3) the change from baseline in mean social function domain score over months 4, 5, and 6 of the 6-month DBTP, as measured by MFIQ • The intercurrent event is adherence to treatment. The treatment effect of interest will be assessed for all randomized subjects enrolled from traditional sites who receive at least 1 dose of IP and have a baseline value and at least 1 post-baseline value of the respective MFIQ domain score, regardless of adherence to treatment. • The summary measure, which is the difference in means of the respective endpoint between the erenumab group and the placebo group	

Hypotheses

The primary clinical hypothesis is that preventive treatment with monthly injections of erenumab is superior to placebo in reducing disability in employed subjects with EM who have previously failed 1 or more migraine preventive treatments.

Overall Design

Study 20180060 is a phase 4, 24-week, prospective, double-blind, randomized, placebo-controlled, multicenter study in the United States (US), evaluating the effect of erenumab on disability and work productivity in employed patients with EM who have previously failed 1 or more migraine preventive treatments. Subjects will enter initial screening (up to 21 days) to determine if they meet Eligibility Criteria Part 1. If Part 1 eligibility criteria are met, subjects will enter baseline (28 days). After subjects complete baseline and are found eligible based on Eligibility Criteria Part 2, they will be enrolled and randomized in a 1:1 ratio to either erenumab 140 mg or placebo. Randomization will be performed separately within traditional sites and decentralized clinical trial site (DCTS). For DCTS, please refer to (Section 5.2.2.1). Subjects will then enter a 24-week DBTP which will conclude with an end-of-study visit at week 24.

Number of Subjects

Approximately 240 subjects from traditional sites will be enrolled in the study, 120 per treatment group. Up to an additional 100 subjects (50 per treatment group) will be

enrolled to pilot DCTS, a clinical trial operating model that enables remote participation in clinical trials (Section 5.2.2.1).

Summary of Subject Eligibility Criteria

Key inclusion criteria include:

- ≥ 18 years of age upon entry into initial screening
- Documented history of migraine with or without aura according to the International Headache Society (IHS) International Classification of Headache Disorders, Third Edition (ICHD-III) for ≥ 12 months
- Has EM defined as history of ≥ 4 and < 15 migraine days and < 15 headache days per month on average during the 3 months prior to initial screening and during baseline
- Employed ≥ 20 hours/week upon entry into initial screening, **stable for at least 3 months in the same job** and has not specified willful termination of employment throughout the duration of the study. Employment is defined as work outside the home, self-employed, or work from home.
- Has ≥ 4 hours of lost productive time in the past month prior to initial screening **(determined by the subject)** and during baseline **(assessed by electronic Diary [eDiary] device). Lost productive time is due to headache/migraine and/or related symptoms.**
- Has total disability score of > 10 as assessed by MIDAS (3-month recall) at initial screening and total disability score of > 3 by modified MIDAS (1-month recall) on day 1 (prior to randomization)
- History of treatment failure with at least 1 preventive treatment category for migraine (see exclusion criterion 214 for treatment category definition). Failure of preventive treatment category for migraine is defined as treatment discontinuation due to lack of efficacy, adverse event, or general poor tolerability.

Key exclusion criteria include:

- Previously treated with any agent (monoclonal antibody or small molecule) targeting the calcitonin gene-related peptide (CGRP) pathway (ligand or receptor) in preventive settings
- History of cluster headache, hemiplegic migraine, or other trigeminal autonomic cephalalgia
- Evidence of substance-related disorders (eg, abuse, misuse, or addiction), addictive disorders (eg, pathological gambling), or "recreational use" of illicit drugs within 12 months prior to initial screening, based on medical records, patient self-report, or positive urine drug test performed during screening (with the exception of prescribed medications such as opioids or barbiturates that may result in a positive urine drug test)
- Taken an opioid and/or opioid-containing analgesic **≥** 4 days during the 1 month prior to initial screening or ≥ 4 days during baseline for any indication
- Taken a butalbital and/or butalbital-containing analgesic **≥** 4 days during the 1 month prior to initial screening **or ≥ 4 days during baseline** for any indication

For a full list of eligibility criteria, please refer to Section 6.1 to Section 6.4.

Treatments

Investigational product (erenumab [140 mg] or placebo) in prefilled syringes (PFS) will be administered by study staff **or subject (refer to Table 7-1)** every 4 weeks during the 24-week treatment period. Subjects participating in the study as part of the DCTS will self-inject the IP in PFS at their own physical location (eg, home) under the observation of the investigator/member of the study team via videoconference, after being trained on day 1 by the qualified study personnel on self-injections.

Procedures

After signing informed consent, subjects will enter the screening period. The screening period is up to 7 weeks and is composed of an initial screening up to 3 weeks (21 days) followed by a 4-week (28 days) baseline. At the day 1 visit, eligible subjects will be enrolled and randomized into the 24-week (6-month) DBTP and will begin to receive IP subcutaneously (SC) every 4 weeks. Subjects will use an eDiary everyday throughout the baseline period and DBTP to report information about their migraine and nonmigraine headaches, other migraine-related symptomatology, medication taken, and complete other clinical outcome assessments (COAs). Subjects will have a wearable device on the wrist to monitor physical activity and sleep and will continuously wear the device throughout the study except when recharging or medically/professionally contraindicated (see Section 9.2.2.2). Subjects will have scheduled monthly study visits throughout the study.

For a full list of study procedures, including the timing of each procedure, please refer to Section 9.2 and the Schedule of Activities in Section 2.2.

Statistical Considerations

The final analysis will be performed when the last subject completes the study or discontinues the study.

Formal statistical hypothesis testing will be performed for subjects enrolled from traditional sites. Statistical analyses for the DCTS will be considered exploratory.

Under the assumption of missing at random (MAR), the primary and secondary endpoints will be analyzed using a linear mixed effects model including treatment group, baseline value, scheduled visit, and the interaction of treatment group with scheduled visit, without any imputation for missing data. The least-square estimate for each treatment group, the treatment difference, 95% CI, and p-value will be reported.

Primary and secondary endpoints for the erenumab 140 mg group versus placebo will be tested using a sequential testing procedure to maintain a family-wise type 1 error rate $\alpha = 0.05$. The order of the endpoints to be tested is prespecified below. If any test is not significant at the $\alpha = 0.05$ level, no further testing will be performed.

1. Primary endpoint: total monthly change from baseline in migraine-related disability over the 6-month DBTP, as measured by monthly modified MIDAS
2. Secondary endpoint: change from baseline in mean MMD over months 4, 5, and 6 of the 6-month DBTP
3. Secondary endpoint: change from baseline in mean monthly average percent overall work impairment over months 4, 5, and 6 of the 6-month DBTP, as measured by WPAI (questions 2, 4, and 5)
4. Secondary endpoint: change from baseline in mean physical function domain score over months 4, 5, and 6 of the 6-month DBTP, as measured by MFIQ
5. Secondary endpoint: change from baseline in mean usual activities domain score over months 4, 5, and 6 of the 6-month DBTP, as measured by MFIQ
6. Secondary endpoint: change from baseline in mean social function domain score over months 4, 5, and 6 of the 6-month DBTP, as measured by MFIQ

Multiple imputation (MI) with the assumption of missing not at random (MNAR) will be used as a sensitivity analysis to handle missing data at each assessment time point for the primary and secondary endpoints, using the analysis of covariance (ANCOVA) model including treatment group and baseline value.

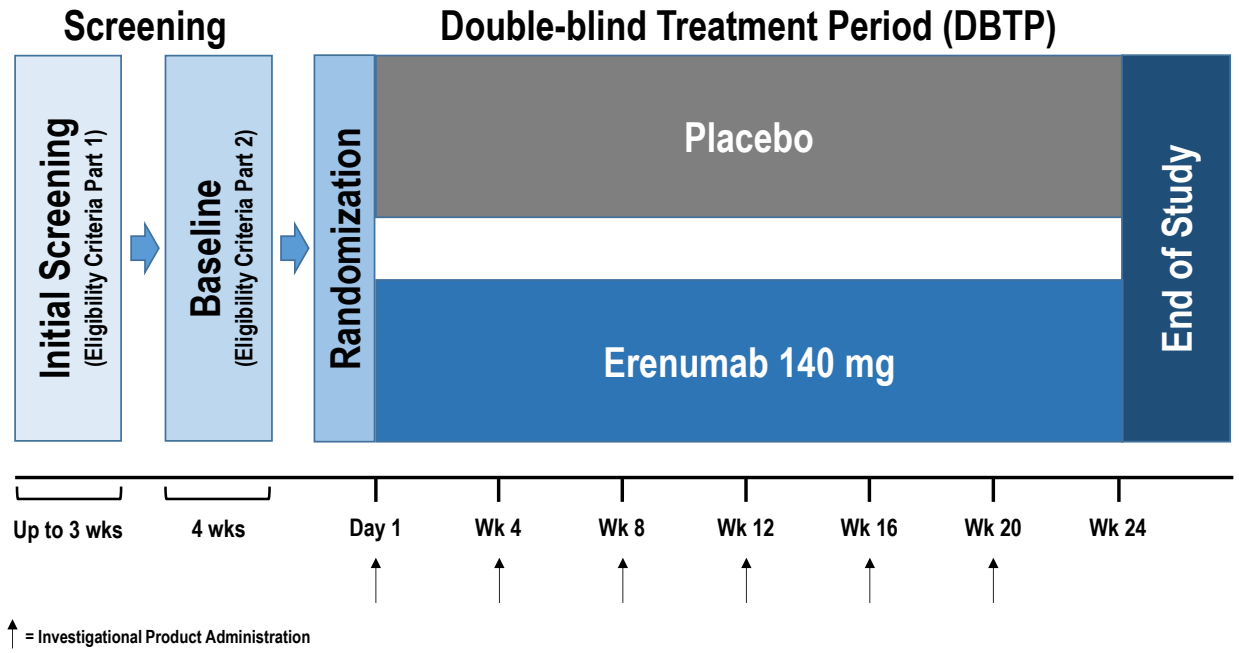
For a full description of statistical analysis methods, please refer to Section 10.

Sponsor Name: Amgen, Inc

2. Study Schema and Schedule of Activities

2.1 Study Schema

Figure 2-1. Study Schema



2.2 Schedule of Activities

Table 2-1. Schedule of Activities

Procedure	Screening Period		Double-blind Treatment Period (weeks)[b]							Notes
	Initial Screening[a]	Baseline								
		D -28 to D -1	D1	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24/ EOS[c]	
GENERAL ASSESSMENTS										
Informed consent	X									
Eligibility Criteria Part 1	X									For a list of criteria, see Sections 6.1 and 6.2.
3-month MIDAS	X									3-month recall; paper format[d]
Employment status	X	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
Demographics	X									
COVID-19 impact assessment		**Weekly**								
Physical measurements	X									Height and weight
Medical history	X									
Neurological medical history	X									
Headache and migraine frequency medical history	X									
Cardiovascular medical history	X									
Cardiac risk factors medical history	X									

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Footnotes after last page of table.

Table 2-1. Schedule of Activities

Procedure	Screening Period		Double-blind Treatment Period (weeks)[b]							Notes
	Initial Screening[a]	Baseline								
		D -28 to D -1	D1	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24/ EOS[c]	
GENERAL ASSESSMENTS (continued)										
Prior migraine preventive medication history	X									
Substance use	X		X							Evidence of substance-related disorders (eg, abuse, misuse, or addiction), addictive disorders (eg, pathological gambling), or "recreational use" of illicit drugs within 12 months prior to initial screening and baseline, based on medical records, patient self-report, or positive urine drug test performed at initial screening (with the exception of prescribed medications such as opioids or barbiturates that may result in a positive urine drug test)
Prior/Concomitant therapies review	X	X	X	X	X	X	X	X	X	(as early as 120 days prior to initial screening)
Eligibility Criteria Part 2			X							For a list of criteria, see Section 6.3 and 6.4.

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Footnotes after last page of table.

Table 2-1. Schedule of Activities

Procedure	Screening Period		Double-blind Treatment Period (weeks)[b]							Notes
	Initial Screening[a]	Baseline								
		D -28 to D -1	Day 1	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24/ EOS[c]	
SAFETY ASSESSMENTS										
Adverse events			X	X	X	X	X	X	X	
Serious adverse events	X	X	X	X	X	X	X	X	X	
Adverse device effects		X	X	X	X	X	X	X	X	
Product complaints		X	X	X	X	X	X	X	X	
LOCAL LABORATORY ASSESSMENTS										
Urine pregnancy test (FOCP only)	X		X	X	X	X	X	X	X	Additional on-treatment pregnancy testing may be performed at the investigator's discretion if there is suspicion that a female subject is pregnant or per local laws and regulations.
Urine drug testing	X									Urine drug testing can be done as needed throughout the study per investigator discretion. Positive urine drug testing that may be reasonably linked to use of an allowable over-the-counter medication may require retesting before eligibility can be considered. In such instances, Amgen medical monitor must be consulted prior to retesting or determining eligibility.

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Footnotes after last page of table.

Table 2-1. Schedule of Activities

Procedure	Screening Period		Double-blind Treatment Period (weeks)[b]							Notes
	Initial Screening[a]	Baseline								
		D -28 to D -1	Day 1	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24/ EOS[c]	
(OPTIONAL) BIOMARKER AND PHARMACOGENETIC ASSESSMENTS										
Biomarker development, blood			X							
Pharmacogenetic studies[e]			X							
HEALTH ECONOMIC ASSESSMENTS										
HRU Questionnaire (24-week recall)			X						X	The HRU questionnaire will have a 24-week recall of prior utilization. For early termination visits, questionnaire assessed at the EOS visit before week 24 should only include HRU recalled since the previous assessment to avoid collecting duplicate information.
CLINICAL OUTCOME ASSESSMENTS										
eDiary		Daily								
Modified MIDAS			X	X	X	X	X	X	X	1-month recall; Assessment on Day 1 should be completed prior to randomization
WPAI		Weekly								

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Footnotes after last page of table.

Table 2-1. Schedule of Activities

Procedure	Screening Period		Double-blind Treatment Period (weeks)[b]							Notes
	Initial Screening[a]	Baseline								
		D -28 to D -1	Day 1	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24/ EOS[c]	
CLINICAL OUTCOME ASSESSMENTS (continued)										
MFIQ			X	X	X	X	X	X	X	
PHQ-9	X		X	X		X			X	Assessment during initial screening is to fulfill eligibility criteria; Paper format during screening[d]
GAD-7			X	X		X			X	
PSQI			X	X		X			X	
ESS			X	X		X			X	
Patient satisfaction at work			X	X		X			X	
PVT			X	X		X			X	PVT should be collected after randomization on Day 1. PVT will not be completed by subjects participating as part of DCTS.
STUDY-RELATED DEVICE ASSIGNMENT										
Assign eDiary device		X								
Assign wearable device		X								See Section 9.2.2.2.
STUDY TREATMENT										
IP administration			X	X	X	X	X	X		

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DCTS = decentralized clinical trial site; ESS = Epworth Sleepiness Scale; GAD-7 = Generalized Anxiety Disorder 7-item Scale; Hep = hepatitis; HRU = Health Resource Utilization; IP = investigational product; MFIQ = Migraine Functional Impact Questionnaire; MIDAS = Migraine Disability Assessment; PHQ-9 = Patient

Health Questionnaire; PSQI = Pittsburgh Sleep Quality Index; PVT = Psychomotor Vigilance Test; Wk = week; WPAI = Work Productivity and Activity Impairment Questionnaire

[a] The initial screening period is up to 3 weeks (21 days) before the baseline period begins.

[b] Each study visit during the double-blind treatment period (DBTP) has a window of ± 3 consecutive calendar days. The baseline period has a window of + 7 consecutive calendar days; the day 1 visit must occur 28 to 35 days after the week -4 visit date. All study visit target dates are to be calculated from the day 1 visit date. All study procedures for a given study visit are to be completed on the same day.

[c] A subject who discontinues the study during the DBTP (before week 24) will complete the assessments of the week 24/EOS visit.

[d] Format of these questionnaires will be electronic for the DCTS (within DCTS hand-held device).

[e] For subjects who provided informed consent for the pharmacogenetic studies, DNA will be obtained from the cell pellet collected in the plasma tube used for the biomarker development sample. Therefore, additional sampling is not required.

3. Introduction

3.1 Study Rationale

The presence of various comorbidities in migraine patients, whether associated or migraine-induced, has been established by numerous studies. These comorbidities contribute to migraine-related disability, impacting work and overall function (Lipton et al, 2013; Stewart et al, 2008). The American Migraine Prevalence and Prevention (AMPP) study of patients with episodic migraine (EM) evaluated several domains of headache-related disability such as work, depression, and anxiety, to name a few, that are frequently affected by migraine. Other studies, though smaller in scale, have demonstrated the impact of migraine on quality and quantity of sleep (Barbanti et al, 2007; Kelman and Rains, 2005).

Closer analyses of impact of migraine on work have not only revealed absence from work, but also reduction in performance also known as presenteeism (Stewart et al, 2008). Relevant components of decreased presenteeism include impaired concentration and feeling of fatigue.

In phase 2 and 3 clinical trials, erenumab-aooe (referred to as erenumab herein) has demonstrated a reduction in monthly migraine days (MMD) as well as migraine-related disability (Dodick et al, 2018; Tepper et al, 2017; Goadsby et al, 2017b). **Separately,** improvement in MMD and migraine-related disability have been associated with improvement in work productivity (Dodick et al, 2016; Lipton et al, 2013). Study 20180060 is being conducted to confirm the effect of erenumab on migraine-related disability (inclusive of aforementioned comorbidities) and work productivity.

Given that this study's focus is on work productivity, the rationale for selecting EM as the target population is as follows. CM has a higher burden of disability and therefore unemployment and under-employment are more prevalent. Additionally, the prior AMPP study referenced above, focused on EM in order to be able to evaluate multiple domains related to work.

3.2 Background

3.2.1 Disease

Migraine is a debilitating disease with worldwide prevalence of approximately 11.7% in the United States (US), 14.6% in Canada, 14.7% in Europe, and 8.4% in Japan (Stovner and Andree, 2010; Lipton et al, 2007; Sakai and Igarashi, 1997). Migraine is

characterized by primary recurrent headaches with or without aura lasting 4 to 72 hours with at least 2 of the following pain characteristics: unilateral, pulsating, moderate or severe intensity, or aggravated by routine physical activity. In addition, the migraine attacks are often accompanied by nausea, vomiting, and sensitivity to light (photophobia) and sound (phonophobia). Depending on the headache frequency, migraine is divided into 2 broad forms: EM and chronic migraine (CM) according to International Classification of Headache Disorders, third edition (ICHD-III). Episodic migraine is defined as migraine with fewer than 14 headache days per month, while CM has 15 or more headache days per month (where at least 8 of those days are migraine days). Episodic migraine and CM share many common features in their clinical presentation, which include headache pain features and associated symptoms. Although EM and CM are somewhat arbitrarily distinguished based on migraine headache frequency, numerous lines of evidence support that they are a continuum of the same disorder. Not only are clinical symptomologies and functional impairments very similar, but functional imaging results demonstrating involvement of similar brain regions support a common underlying pathophysiology (Aurora and Wilkinson, 2007; Afridi et al, 2005; Aurora et al, 2005; Welch et al, 2001). Regardless of classification as EM or CM, migraine has life altering impact beyond physical symptoms and debilitation. Migraine-related disability has social, psychological, and economical implications (Lipton et al, 2013; Lipton et al, 2007). The AMPP and Chronic Migraine Epidemiology and Outcomes (CaMEO) studies demonstrated the impact of migraine-related disability on various elements of daily function as well as work productivity (Lipton et al, 2013; Lipton et al, 2007).

Only approximately 12% of patients with migraine receive any preventive therapy due to limited efficacy and significant tolerability and safety issues with available preventive therapies. Migraine prevention is an area of large unmet medical need.

3.2.2 Amgen Investigational Product Background: Erenumab

Erenumab is a human immunoglobulin G2 (IgG2) monoclonal antibody that is directed against the canonical calcitonin gene-related peptide (CGRP) receptor complex and inhibits the action of CGRP. Calcitonin gene-related peptide belongs to the calcitonin family of peptides and is expressed in both the central and peripheral nervous systems. It is prominently involved in the pathophysiology of migraine through nociceptive modulation, in the trigeminovascular system (Goadsby et al, 2002; Tajti et al, 1999). Nonclinical studies with erenumab demonstrated that it binds to and antagonizes both

human and cynomolgus monkey CGRP receptors with high affinity and potency. Erenumab has been developed for the prevention of migraine in adults based on the observed long serum half-life in humans (28 days), clinical data demonstrating that small molecule CGRP receptor antagonists are effective in acute migraine reversal (Ho et al, 2008a; Ho et al, 2008b), prevention (Ho et al, 2014), and the strong rationale for CGRP's association with migraine pathophysiology (Goadsby et al, 2017a; Sun et al, 2016; Bellamy et al, 2006; Sarchielli et al, 2006; Juhasz et al, 2005; Petersen et al, 2005; Lassen et al, 2002; Tajti et al, 1999; Gallai et al, 1995; Goadsby et al, 1990; Goadsby et al, 1988).

As of the date of approval of this protocol, erenumab 70 mg and 140 mg subcutaneously (SC) every 4 weeks (Q4W) or once monthly (QM) have been approved in the US, Europe, Australia, and Switzerland for the prevention of migraine in adults with additional ongoing approvals globally. **As of the date of approval of this protocol, erenumab 70 mg and 140 mg subcutaneously (SQ), every 4 weeks (Q4W) or once monthly (QM) have been approved in more than 60 countries including US, EU, and Australia.**

A detailed description of the chemistry, pharmacology, efficacy, and safety of erenumab can be found in the Investigator's Brochure.

3.3 Benefit/Risk Assessment

Erenumab 140 mg has demonstrated a favorable benefit-risk profile for prevention of migraine in adults in pivotal and supportive phase 2 and 3 studies.

The key benefits of erenumab for prevention of migraine headaches in adults consist of confirmatory results that include reduction in mean MMDs, reduction in acute medication use, and favorable tolerability and low treatment discontinuation rate, as well as supportive results that include convenience, and improvements in clinical outcome assessments (COA) (Migraine Physical Function Impact Diary [MPFID], Migraine Disability Assessment [MIDAS], and Headache Impact Test-6 [HIT-6]).

Overall, the safety profile of erenumab has been favorable in clinical trials. A limited number of adverse drug reactions (injection site reactions, constipation, muscle spasm, and pruritis) have been identified at low frequencies (< 5%) in clinical trials. In post-marketing settings, hypersensitivity reactions (including rash, angioedema, and anaphylactoid reactions) and constipation with serious complications have been reported. In conclusion, erenumab 140 mg addresses an unmet need as an effective,

safe, and tolerable preventive treatment of migraine. The key benefits of erenumab outweigh the risks in this population.

Reference should be made to the Investigator's Brochure and Prescribing Information, where Aimovig® is approved, for further data on erenumab.

4. Objectives, Endpoints and Hypotheses

4.1 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the effect of erenumab compared to placebo on disability in employed subjects with episodic migraine (EM) who have previously failed 1 or more migraine preventive treatments	• Sum of monthly changes from baseline in modified Migraine Disability Assessment (MIDAS) total score over the 6-month double-blind treatment period (DBTP)
Primary Estimand	
The primary estimand for the primary objective on migraine-related disability consists of: • The target population, which includes employed subjects with EM who have previously failed 1 or more migraine preventive treatments • The endpoint, which is the sum of monthly changes from baseline in modified MIDAS total score over the 6-month DBTP • The intercurrent event is adherence to treatment. The treatment effect of interest will be assessed for all randomized subjects enrolled from traditional sites who receive at least 1 dose of investigational product (IP) and have a baseline value and at least 1 post-baseline value of modified MIDAS total score, regardless of adherence to treatment • The summary measure, which is the difference in means of the endpoint between the erenumab group and the placebo group The primary estimand is the difference in means between erenumab and placebo of the sum of monthly changes from baseline in modified MIDAS total score over the 6-month DBTP in employed subjects with EM who have previously failed 1 or more migraine preventive treatments and who are randomized, receive at least 1 dose of IP, and have a baseline value and at least 1 post-baseline value of modified MIDAS total score, regardless of adherence to treatment.	
Secondary	
• To evaluate the effect of erenumab compared to placebo on monthly migraine days (MMD) in employed subjects with EM who have previously failed 1 or more migraine preventive treatments	• Change from baseline in mean MMD over months 4, 5, and 6 of the 6-month DBTP

Objectives	Endpoints
Secondary (Continued)	
The estimand for the secondary objective on MMD consists of: • The target population, which includes employed subjects with EM who have previously failed 1 or more migraine preventive treatments • The endpoint, which is the change from baseline in mean MMD over months 4, 5, and 6 of the 6-month DBTP • The intercurrent event is adherence to treatment. The treatment effect of interest will be assessed for all randomized subjects enrolled from traditional sites who receive at least 1 dose of IP and have a baseline value and at least 1 post-baseline value of MMD, regardless of adherence to treatment. • The summary measure, which is the difference between the mean of the endpoint for the erenumab group and the placebo group The estimand is the difference in means between erenumab and placebo of the change from baseline in mean MMD over months 4, 5, and 6 of the 6-month DBTP in employed subjects with EM who have previously failed 1 or more migraine preventive treatments and who are randomized, receive at least 1 dose of IP, and have a baseline value and at least 1 post-baseline value of MMD, regardless of adherence to treatment.	
• To evaluate the effect of erenumab compared to placebo on work impairment in employed subjects with EM who have previously failed 1 or more migraine preventive treatments	• Change from baseline in mean monthly percent work impairment over months 4, 5, and 6 of the 6-month DBTP, as measured by the Work Productivity and Activity Impairment Questionnaire (WPAI): Migraine V2.0 (WPAI questions 2, 4, and 5) Note: the monthly percent work impairment equals to the arithmetic mean of the observed weekly percent work impairment over the monthly interval.
The estimand for the secondary objective on work impairment consists of: • The target population, which includes employed subjects with EM who have previously failed 1 or more migraine preventive treatments • The endpoint, which is the change from baseline in mean monthly percent work impairment over months 4, 5, and 6 of the 6-month DBTP • The intercurrent event is adherence to treatment. The treatment effect of interest will be assessed for all randomized subjects enrolled from traditional sites who receive at least 1 dose of IP and have a baseline value and at least 1 post-baseline value of monthly percent work impairment, regardless of adherence to treatment. • The summary measure, which is the difference in means of the endpoint between the erenumab group and the placebo group	

Objectives	Endpoints
Secondary (Continued)	
The estimand is the difference in means between erenumab and placebo of the change from baseline in mean monthly percent work impairment over months 4, 5, and 6 of the 6-month DBTP in employed subjects with EM who have previously failed 1 or more migraine preventive treatments and who are randomized, receive at least 1 dose of IP, and have a baseline value and at least 1 post-baseline value of monthly percent work impairment, regardless of adherence to treatment.	
• To evaluate the effect of erenumab compared to placebo on physical function, usual activities, and social function in employed subjects with EM who have previously failed 1 or more migraine preventive treatments	• Change from baseline in mean physical function domain score over months 4, 5, and 6 of the 6-month DBTP, as measured by Migraine Functional Impact Questionnaire (MFIQ) • Change from baseline in mean usual activities domain score over months 4, 5, and 6 of the 6-month DBTP, as measured by MFIQ • Change from baseline in mean social function domain score over months 4, 5, and 6 of the 6-month DBTP, as measured by MFIQ
The estimand for the secondary objective on function (physical, usual activities, and social) consists of: • The target population, which includes employed subjects with EM who have previously failed 1 or more migraine preventive treatments • The endpoints include: 1) the change from baseline in mean physical function domain score over months 4, 5, and 6 of the 6-month DBTP, as measured by MFIQ 2) the change from baseline in mean usual activities domain score over months 4, 5, and 6 of the 6-month DBTP, as measured by MFIQ 3) the change from baseline in mean social function domain score over months 4, 5, and 6 of the 6-month DBTP, as measured by MFIQ • The intercurrent event is adherence to treatment. The treatment effect of interest will be assessed for all randomized subjects enrolled from traditional sites who receive at least 1 dose of IP and have a baseline value and at least 1 post-baseline value of the respective MFIQ domain score, regardless of adherence to treatment. • The summary measure, which is the difference in means of the respective endpoint between the erenumab group and the placebo group	

Objectives	Endpoints
Exploratory	
• To evaluate the effect of erenumab compared to placebo on work impairment in employed subjects with EM who have previously failed 1 or more migraine preventive treatments	• Change from baseline in monthly average percent overall work impairment at each monthly assessment time point during the 6-month DBTP, as measured by the WPAI (questions 2, 4, and 5)
• To evaluate the effect of erenumab compared to placebo on MMD in employed subjects with EM who have previously failed 1 or more migraine preventive treatments	• Change from baseline in MMD at each monthly assessment time points during the 6-month DBTP
• To evaluate the effect of erenumab compared to placebo on function and quality of life in employed subjects with EM or who have previously failed 1 or more migraine preventive treatments	• Change from baseline in mean emotional function domain score over months 4, 5, and 6 of the 6-month DBTP, as measured by MFIQ • Change from baseline in mean overall impact on usual activities global item score over months 4, 5, and 6 of the 6-month DBTP, as measured by MFIQ • Change from baseline in MFIQ domain scores of function (physical, usual activities, social, and emotional) and overall impact on usual activities global item score at each monthly assessment time point during the 6-month DBTP • Change from baseline in depression at months 1, 3, and 6 of the 6-month DBTP, as measured by the Patient Health Questionnaire (PHQ-9) total score • Change from baseline in anxiety at months 1, 3, and 6 of the 6-month DBTP, as measured by Generalized Anxiety Disorder 7-item Scale (GAD-7) total score • Change from baseline in insomnia at months 1, 3, and 6 of the 6-month DBTP, as measured by the Pittsburgh Sleep Quality Index (PSQI) total score

Objectives	Endpoints
Exploratory (Continued)	
	• Change from baseline in excessive daytime sleepiness at months 1, 3, and 6 of the 6-month DBTP, as measured by the Epworth Sleepiness Scale (ESS) total score • Change from baseline in monthly average activity level during and between migraine days at each monthly assessment time point during the 6-month DBTP, as measured by a wearable • Change from baseline in patient satisfaction at work at months 1, 3, and 6 of the 6-month DBTP, as measured by the questions in Section 9.2.2.1.8
• To describe the effect of erenumab on migraine-related health resource utilization (HRU) in employed subjects with EM who have previously failed 1 or more migraine preventive treatments	• Occurrence of at least 1 migraine-related hospitalization or outpatient HRU during the 6-month DBTP • Occurrence of at least 1 migraine-related hospitalization during the 6-month DBTP • Occurrence of at least 1 migraine-related outpatient HRU during the 6-month DBTP • Occurrence of at least 1 migraine-related outpatient emergency room visit during the 6-month DBTP • Occurrence of at least 1 migraine-related outpatient urgent care visit during the 6-month DBTP • Occurrence of at least 1 migraine-related outpatient clinic visit during the 6-month DBTP
• To evaluate the effect of erenumab compared to placebo on attention in employed subjects with EM who have previously failed 1 or more migraine preventive treatments	• Change from baseline in mean reaction time at months 1, 3, and 6 of the 6-month DBTP, as measured by the Psychomotor Vigilance Test (PVT) • Change from baseline in number of lapses and errors at months 1, 3, and 6 of the 6-month DBTP, as measured by PVT

4.2 Hypotheses

The primary clinical hypothesis is that preventive treatment with monthly injections of erenumab is superior to placebo in reducing disability in employed subjects with EM who have previously failed 1 or more migraine preventive treatments.

5. Study Design

5.1 Overall Design

Study 20180060 is a phase 4, 24-week, prospective, double-blind, randomized, placebo-controlled, multicenter study in the US, evaluating the effect of erenumab on disability and work productivity in employed patients with EM who have previously failed 1 or more migraine preventive treatments. Subjects will enter initial screening (up to 21 days) to determine if they meet Eligibility Criteria Part 1. If Part 1 eligibility criteria are met, subjects will enter the baseline (28 days). After subjects complete the baseline and are found eligible based on Eligibility Criteria Part 2, they will be enrolled and randomized in a 1:1 ratio to either erenumab 140 mg or placebo. Randomization will be performed separately within traditional sites and the decentralized clinical trial site (DCTS). For the DCTS, please refer to Section 5.2.2.1. Subjects will then enter a 24-week DBTP which will conclude with an end-of-study visit at week 24.

The overall study design is described by a study schema in Section 2.1. The endpoints are defined in Section 4.1.

5.2 Number of Subjects

Approximately 240 subjects from traditional sites will be enrolled in the study, 120 per treatment group. Up to an additional 100 subjects (50 per treatment group) will be enrolled to pilot DCTS, a clinical trial operating model that enables remote participation in clinical trials (Section 5.2.2.1).

Subjects in this clinical investigation shall be referred to as “subjects”. For the sample size justification, see Section 10.1.

5.2.1 Replacement of Subjects

Subjects who are withdrawn or removed from treatment or the study will not be replaced.

5.2.2 Number of Sites

Approximately 31 investigative sites (30 traditional sites plus 1 DCTS) in the US will be included in the study. Sites that do not enroll subjects within 3 months of site initiation may be closed.

5.2.2.1 Decentralized Clinical Trials Site (DCTS)

The DCTS is a remote study model that integrates telemedicine technology into the clinical research process and supports management of research activities, including data collection. As part of this model, study visits are completed using the DCTS technology platform. This 21 Code of Federal Regulations (CFR) Part 11 compliant software interface facilitates recruitment, enrollment, and study data collection within a single cloud-based technology. It connects subjects to their investigators and study team through a study-issued smartphone.

Decentralizing research studies from traditional site-based centers, making them "site-less," aims to eliminate barriers to participation including inaccessibility due to geography and the inconvenience of traveling to site visits. A DCTS complies with all regulatory requirements applicable to study investigators, as delineated in 21 CFR 312 and International Council for Harmonisation (ICH) E6 (R2). As such, it does not assume any Sponsor or Contract Research Organization (CRO) obligations.

5.3 End-of-Study

5.3.1 End-of-Study Definition

Primary Completion: The primary completion date is defined as the date when the last subject is assessed or receives an intervention for the final collection of data for the primary endpoint(s), whether the study concluded as planned in the protocol or was terminated early.

The primary completion date is the date when the last subject has completed the assessments for week 24 (month 6) or discontinues study.

If the study concludes prior to the primary completion date originally planned in the protocol (ie, early termination of the study), then the primary completion will be the date when the last subject is assessed or receives an intervention for evaluation in the study (ie, last subject last visit).

End-of-Study: The end-of-study date is defined as the date when the last subject across all sites is assessed or receives an intervention for evaluation in the study (ie, last subject last visit), following any additional parts in the study (eg, long-term follow-up), as applicable. For this study, the end-of-study date is the same as the primary completion date.

5.3.2 Study Duration for Subjects

The total study duration for subjects who successfully complete the study will be up to 31 weeks.

5.4 Justification for Investigational Product Dose

The erenumab dose being used in this study is in accordance with the term of its marketing authorization in the US. The 140 mg dose has been selected as the treatment dose because it has demonstrated greater efficacy in phase 2 and 3 clinical trials. In the Study to Evaluate the Efficacy and Safety of Erenumab in Migraine Prevention (STRIVE) study of EM patients (phase 3; 20120296), erenumab 140 mg treatment arm experienced statistically significant reduction from baseline in MMD as compared with 70 mg and placebo (Goadsby et al, 2017b). Furthermore, in a post-hoc analysis of STRIVE, patients with ≥ 2 prior treatment failures in the 140 mg erenumab arm had an average MMD reduction nearly twice as much as those in the 70 mg erenumab arm (Goadsby et al, 2017c). In the phase 3b LIBERTY study (A Study Evaluating the Effectiveness of AMG 334 Injection in Preventing Migraines in Adults Having Failed Other Therapies) of EM patients who had failed 2 to 4 prophylactic migraine treatments and were treated with either erenumab 140 mg or placebo, 30% demonstrated a 50% or greater reduction in their individual baseline MMD (primary endpoint) compared with placebo. Also, erenumab 140 mg reduced MMD as compared with placebo (secondary endpoint) (Reuter et al, 2018).

5.5 Patient Input on Study Design

Patient input was not collected during study design.

6. Study Population

Investigators will be expected to maintain a screening log of all potential study candidates that includes limited information about the potential candidate (eg, date of screening).

Eligibility criteria will be evaluated during initial screening (Part 1) and determines eligibility for subjects to enter baseline. Additional (Part 2) eligibility criteria will be evaluated on day 1 (pre-enrollment) for those who successfully met eligibility criteria during initial screening and completed the 4-week (28 days) baseline for entry into the double-blind treatment period.

Before any study-specific activities/procedures, the appropriate informed consent must be obtained (see Section 12.3).

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions will not be provided.

6.1 Inclusion Criteria Part 1

Subjects are eligible to be included in the study only if all of the following criteria apply:

101 Provided informed consent prior to initiation of any study-specific activities/procedures

102 ≥ 18 years of age upon entry into initial screening

103 Documented history of migraine with or without aura according to the International Headache Society (IHS) ICHD-III for ≥ 12 months

104 Has EM defined as history of ≥ 4 and < 15 migraine days and < 15 headache days per month on average during the 3 months prior to initial screening (see Section 12.1 for definition of headache/migraine days)

106 Has ≥ 4 hours of lost productive time **due to headache/migraine and/or related symptoms** in the past month prior to initial screening **as determined by subject.**

107 Has total disability score of > 10 as assessed by MIDAS (3-month recall) at initial screening

108 History of treatment failure with at least 1 preventive treatment category for migraine (see exclusion criterion 214 for treatment category definition). Failure of preventive treatment category for migraine is defined as treatment discontinuation due to lack of efficacy, adverse event, or general poor tolerability.

115 Employed ≥ 20 hours/week upon entry into initial screening, **stable for at least 3 months in the same job** and has not specified willful termination of employment throughout the duration of the study. Employment is defined by work outside the home, self-employed, or works from home.

6.2 Exclusion Criteria Part 1

Subjects are excluded from the study if any of the following criteria apply:

Disease Related

201 Older than 50 years of age at migraine onset

202 History of cluster headache, hemiplegic migraine, or other trigeminal autonomic cephalalgia

Other Medical Conditions

203 Currently diagnosed with fibromyalgia and/or chronic pelvic pain

204 History of major psychiatric disorder (such as schizophrenia or other psychotic disorders, bipolar disorder, obsessive-compulsive disorder, post-traumatic stress disorder), or current evidence of moderately severe depression based on a PHQ-9 total score of ≥ 15 at initial screening

205 Malignancy, except non-melanoma skin cancers, cervical, or breast ductal carcinoma in situ, within the last 5 years

206 Known human immunodeficiency virus (HIV) infection

207 Known hepatic disease or evidence of acute or chronic hepatitis B or hepatitis C

231 Evidence of substance-related disorders (eg, abuse, misuse, or addiction), addictive disorders (eg, pathological gambling), or "recreational use" of illicit drugs within 12 months prior to screening, based on medical records, patient self-report, or positive urine drug test performed during initial screening (with the exception of prescribed medications such as opioids or barbiturates that may result in a positive urine drug test)

211 Known hypersensitivity to any of the products or components to be administered during dosing

236 Taken an opioid and/or opioid-containing analgesic **≥** 4 days during the 1 month prior to initial screening for any indication

237 Taken a butalbital and/or butalbital-containing analgesic **≥** 4 days during the 1 month prior to initial screening for any indication

Prior Therapy

234 Previously treated with any agent (monoclonal antibody or small molecule) targeting the CGRP pathway (ligand or receptor) in preventive settings

214 No therapeutic response in preventive treatment of migraine after an adequate therapeutic trial with ≥ 3 of the following medication categories:

- Category 1: Topiramate
- Category 2: Other antiepileptics (eg, divalproex sodium, sodium valproate, carbamazepine, levetiracetam)
- Category 3: Beta blockers
- Category 4: Tricyclic antidepressants
- Category 5: Other antidepressants (eg, serotonin-norepinephrine reuptake inhibitors, selective serotonin-reuptake inhibitors)
- Category 6: Calcium channel blockers (eg, verapamil, amlodipine, cinnarizine, lomerizine) or calcium antagonists (eg, flunarizine)
- Category 7: Angiotensin receptor blockers (eg, candesartan) or angiotensin-converting enzyme (ACE) inhibitors (eg, lisinopril)
- Category 8: Botulinum toxin
- Category 9: Other drugs used for migraine prevention

No therapeutic response is defined as no reduction in headache frequency, duration, or severity after administration of the medication for at least 6 weeks at the generally-accepted therapeutic dose(s) and is based on the investigator's assessment.

The following scenarios do not constitute lack of therapeutic response:

- Lack of sustained response to a medication
- Failure to tolerate a therapeutic dose

Concomitant Therapy

215 Use of an excluded medication/device or procedure (refer to Section 7.1.7 for the list of excluded medications, devices, or procedures and corresponding time period for exclusion)

Prior/Concurrent Clinical Study Experience

235 Currently receiving treatment in another investigational device or drug study, or less than 30 days or 5 half-lives (whichever is longer) since ending treatment on another investigational device or drug study(ies). Other investigational procedures while participating in this study are excluded.

Other Exclusions

217 Female subject is pregnant or breastfeeding or planning to become pregnant or breastfeed during treatment and for an additional 16 weeks after the last dose of IP

218 Female subject of childbearing potential is unwilling to use an acceptable method of effective contraception during treatment and for an additional 16 weeks after the last dose of IP. Refer to Section 12.5 for additional contraceptive information.

219 Female subject of childbearing potential has a positive pregnancy test assessed at screening by a urine pregnancy test

220 Likely to be unavailable or unable to complete all protocol-required study visits or procedures, and/or to comply with all required study procedures to the best of the subject and investigator's knowledge

221 History or evidence of any other clinically significant disorder, condition or disease (with the exception of those outlined above) that, in the opinion of the investigator or Amgen physician, if consulted, would pose a risk to subject safety or interfere with the study evaluation, procedures or completion

222 Related to investigational study site staff or investigator

6.3 Inclusion Criteria Part 2

Subjects will be assessed at the end of the baseline period and prior to enrollment into DBTP.

Based on information collected through the electronic diary (eDiary) during baseline, the following requirements must be met:

109 Has EM defined as ≥ 4 and < 15 migraine days and < 15 headache days during baseline (see Section 12.1 for definition of headache/migraine days)

110 Employed ≥ 20 hours/week upon entry into baseline and has not specified willful termination of employment throughout the duration of the study. Employment is defined by work outside the home, self-employed, or works from home.

111 Has ≥ 4 hours of lost productive time **due to headache/migraine and/or related symptoms** in the past month during baseline as assessed on Day 1 **by eDiary device** (prior to randomization)

112 Has total disability score of > 3 as assessed by modified MIDAS (1-month recall) during baseline as assessed on Day 1 (prior to randomization)

114 Demonstrated at least 75% compliance with the eDiary and had at least 3 WPAI measurements during baseline

6.4 Exclusion Criteria Part 2

Subjects are excluded from the study if after baseline any of the following criteria apply:

223 Change in the regimen of current migraine preventive treatment or a concomitant medication that may have migraine prevention effects during baseline

224 Taken an opioid and/or opioid-containing analgesic ≥ 4 days during baseline for any indication

225 Taken a butalbital and/or butalbital-containing analgesic ≥ 4 days during baseline for any indication

226 Development of unstable or clinically significant medical condition that, in the opinion of the investigator, would pose a risk to subject safety or interfere with the study evaluation, procedures, or completion

227 Evidence of substance-related disorders (eg, abuse, misuse, or addiction), addictive disorders (eg, pathological gambling), or "recreational use" of illicit drugs at baseline based on medical records or patient self-report

228 Female subject is pregnant or planning to become pregnant during treatment and for an additional 16 weeks after the last dose of IP

229 Female subject of childbearing potential has a positive pregnancy test assessed at day 1 by a urine pregnancy test

230 Likely to be unavailable or unable to complete all protocol-required study visits or procedures, and/or to comply with all required study procedures to the best of the subject and investigator's knowledge

6.5 Subject Enrollment

Before subjects begin participation in any study-specific activities/procedures, Amgen requires a copy of the site's written institutional review board/independent ethics committee (IRB/IEC) approval of the protocol, informed consent form, and all other subject information and/or recruitment material, if applicable (see Section 12.3).

The subject must personally sign and date the IRB/IEC and Amgen approved informed consent before commencement of study-specific procedures.

A subject is considered enrolled when the investigator decides that the subject has met all eligibility criteria. The investigator is to document this decision and date, in the subject's medical record/source documentation and in/on the enrollment case report form (CRF).

Upon completion of baseline period procedures, the subject is evaluated by the investigator, and if the subject meets all additional (Part 2) eligibility (inclusion: 109 through 114; exclusion: 223 through 230) criteria he/she is subsequently enrolled

and randomized to a treatment regimen. Subjects who do not meet additional eligibility criteria will be considered screen failures.

Each subject who enters into the screening period for the study (screening period starts when the subject signs and dates the informed consent form) receives a unique subject identification number before any study-related activities/procedures are performed. The subject identification number will be assigned via interactive response technology (IRT). This number will be used to identify the subject throughout the clinical study and must be used on all study documentation related to that subject.

The subject identification number must remain constant throughout the entire clinical study; it must not be changed after initial assignment, including if a subject is rescreened. This number will not be the same as the randomization number assigned for the study.

6.6 Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently enrolled in the study. A minimal set of screen failure information will be collected that includes demography, screen failure details, eligibility criteria, and any serious adverse events.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once if the condition that led to screen failure is expected to be transient. Refer to Section 9.1.1.

7. Treatments

Study treatment is defined as any IP(s), non-IP(s), placebo, or medical device(s) intended to be administered to a study subject according to the study protocol.

The Investigational Product Instruction Manual (IPIM), a document external to this protocol, contains detailed information regarding the storage, preparation, destruction, and administration of each treatment shown in Table 7-1.

7.1 Treatment Procedures

7.1.1 Investigational Products

Table 7-1. Study Treatments

Study Treatment Name	Amgen Investigational Product[a]: Erenumab	Placebo
Dosage Formulation	Erenumab will be supplied as a 70 mg/mL solution formulated with sodium acetate, sucrose, and polysorbate 80.	Placebo will be presented in identical containers and stored/packaged the same as erenumab.
Unit Dose Strength(s)/ Dosage Level(s) and Dosage Frequency	140 mg once every 4 weeks (2 consecutive injections of 70 mg)	Placebo once every 4 weeks (2 consecutive injections)
Route of Administration	SC injection	SC injection
Accountability	The quantity, start date, start time, injection site, and box number(s) of IP are to be recorded on each subject's CRF.	
Dosing Instructions	Treatment doses to be administered at study visits by authorized investigational site study staff **or subject (as appropriate, with Sponsor approval). Subjects enrolled by the DCTS will be permitted to self-inject IP in PFS at their own physical location (eg, home) under the observation of the investigator/member of the study team via videoconference, after being trained on day 1 by the qualified study personnel on self-injections**. Subjects enrolled by the DCTS will be permitted to self-inject the IP in PFS at their own physical location (eg, home) under the observation of the investigator/member of the study team via videoconference, after being trained on day 1 by the qualified study personnel on self-injections. **Subjects enrolled at other sites may need to conduct self-injection after training by qualified personnel, as appropriate (eg, due to COVID-19 visit restrictions).** The 140 mg dose is administered as 2 consecutive SC injections of 70 mg each. The anatomical sites for administration of IP are the upper arm, upper thigh, or abdomen.	
Device	PFS	

CRF = case report form; DCTS = decentralized clinical trial site; IP = investigational product; PFS = prefilled syringe; SC = subcutaneous
[a] Erenumab will be manufactured and packaged by Amgen and distributed using Amgen clinical study drug distribution procedures.

7.1.2 Non-investigational Products

Not applicable.

7.1.3 Medical Devices

The following investigational medical device(s) provided by Amgen for use in this study are the prefilled syringe (PFS) (Table 7-1).

The IP PFS is a single-use, disposable, handheld manual injection device at a fixed dose of 70 mg/mL in a 1 mL deliverable volume. It will be administered as 2 consecutive SC injections for 140 mg/mL dosing.

Additional details are provided in the IPIM.

Other non-investigational medical devices may be used in the conduct of this study as part of standard care.

A wearable device that measures physical activity and other associated parameters will be used throughout the study. Any adverse events associated with the wearable device (eg, allergic reaction to components of the instrument) will be captured in the Events CRF as a procedure-related event.

7.1.4 Other Protocol-required Therapies

There are no other protocol-required therapies in this study.

7.1.5 Other Treatment Procedures

There are no other treatment procedures in this study.

7.1.6 Product Complaints

A product complaint is any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a drug(s) or device(s) after it is released for distribution to market or clinic by either Amgen or by distributors and partners for whom Amgen manufactures the material.

This includes any IP, device, or combination product(s) provisioned and/or repackaged/modified by Amgen (eg, wearable device that measures physical activity and sleep).

Any product complaint(s) associated with an IP(s), devices(s), or combination product(s) supplied by Amgen are to be reported according to the instructions provided in the IPIM.

7.1.7 Excluded Treatments, Medical Devices, and/or Procedures During Study Period

Concomitant treatment with up to 2 oral migraine preventive medication**s** is allowed under the following conditions:

(1) Drug regimen (ie, formulation, frequency of use, route, dose) is stable for ≥ 2 months prior to baseline period start

(2) Drug regimen is at generally accepted dose, frequency and route for its use in migraine

(3) Drug regimen is not anticipated to change during baseline period or post-randomization (ie, during the subject's study participation)

Examples of such medications include:

- Antiepileptics (eg, divalproex sodium, sodium valproate, topiramate, carbamazepine, levetiracetam)
- Angiotensin receptor blockers (eg, candesartan) or ACE inhibitors (eg, lisinopril)
- Beta blockers
- Calcium channel blockers (eg, verapamil, amlodipine, cinnarizine) or calcium antagonists (eg, flunarizine)
- Tricyclic antidepressants
- Other antidepressants (eg, serotonin-norepinephrine reuptake inhibitors, selective serotonin-reuptake inhibitors)

Other drugs used for migraine prevention (eg, clonidine, guanfacine, methysergide, cyproheptadine, pizotifen, butterbur, feverfew, magnesium [≥ 500 mg/day], riboflavin [≥ 100 mg/day])

Table 7-2. Excluded Treatments, Medical Devices, and Procedures

Prohibited Medications	**Time Period for Exclusion**
Frequent use of an allowed acute medication for migraine in a pattern that could be considered more consistent with its use as a preventive	2 months before the start of the screening period and throughout the study
Use of the following acute medications for the acute treatment of migraine for **≥** 4 days/month Barbiturates and/or butalbital-containing analgesics Opioid and/or opioid-containing analgesics**,** CBD-containing products anticipated to have a systemic effect (eg, ingested or inhaled products)	**1** month before the start of the screening period and throughout the study
Investigational medications	30 days or 5 half-lives (whichever is longer) before the start of the screening period and throughout the study
Botulinum toxin (in the head and/or neck region)	4 months before the start of the screening period and throughout the study
Prohibited Procedures or Devices	**Time Period for Exclusion**
For any indication Infusion Therapy (ie, steroids, valproate sodium, dihydroergotamine) Note: infusion therapy may be allowed during DBTP if medically justified	3 months before the start of the screening period and throughout the study

Prohibited Medications	Time Period for Exclusion
For any indication Devices (such as stimulation devices), or procedures (such as nerve blocks **affecting head and neck region** or psychotherapy).	3 months before the start of the screening period and throughout the study
Cognitive Behavioral Therapy NOTE: Subjects on a stable, maintenance phase of CBT for migraine will be allowed to participate. Stable, maintenance phase of CBT is defined as ≥ 6 weekly or biweekly sessions administered by adequately trained psychologists and only "booster" sessions at a monthly, bimonthly or quarterly frequency at least 3 months before the start of the screening period	3 months before the start of the screening period and throughout the study

ACE = angiotensin-converting-enzyme; **CBD = cannabidiol;** CBT = cognitive behavioral therapy; NSAID = nonsteroidal anti-inflammatory drugs

7.2 Method of Treatment Assignment

Subjects will be enrolled and randomized in a 1:1 ratio to either erenumab or placebo. Randomization will be performed separately within traditional sites and DCTS.

The randomization will be performed by IRT, and the randomization number will be assigned by IRT and appear on the IRT randomization document. The randomization number is different than the subject identification number and will not be utilized by the site as a subject identifier.

The randomization date is to be documented in the subject's medical record/source documentation and on the enrollment CRF.

7.3 Blinding

This is a double-blind study. Treatment assignment will be blinded to all subjects, site personnel, and Amgen as described below.

7.3.1 Site Personnel Access to Individual Treatment Assignments

A subject's treatment assignment is to only be unblinded by the investigator when knowledge of the treatment is essential for the further management of the subject on this study or may potentially impact the safety of the subject. Unblinding at the study site for any other reason will be considered a protocol deviation. It is encouraged that the Amgen Trial Manager be notified before the blind is broken unless the investigator believes that identification of the study treatment is required for a medical emergency. If this is not possible, the Amgen Trial Manager must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and CRF, as applicable.

7.3.2 Access to Individual Subject Treatment Assignments by Amgen or Designees

Blinded individuals will not have access to unblinded information until the study is formally unblinded. Unblinding and potentially unblinding information is not to be distributed to the study team, investigators or subjects prior to the study being formally unblinded (eg, the formal unblinding may occur at the final analysis rather than during the primary analysis) except as specified (eg, Section 7.3.1).

7.4 Dose Modification

7.4.1 Dose-cohort Study Escalation/De-escalation and Stopping Rules

There will be no dose changes or dose stopping rules as part of this study.

7.4.2 Dosage Adjustments, Delays, Rules for Withholding or Restarting, Permanent Discontinuation

Dose adjustments are not permitted.

7.4.3 Hepatotoxicity Stopping and Rechallenge Rules

Refer to Section 12.7 for details regarding drug-induced liver injury guidelines, as specified in the *Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009*.

7.5 Preparation/Handling/Storage/Accountability

Guidance and information on preparation, handling, storage, accountability, destruction, or return of the IP and/or device during the study are provided in the IPIM.

For DCTS, the Sponsor will supply the IP to the DCTS or the designee. The IP will then be stored in a temperature-controlled environment until ready to be allocated. The IP and all required supplies will be provided to the subjects via direct-to-patient shipments. Shipments will be confirmed and documented as delivered by the study staff. The IP will be confirmed as received in good condition and within the acceptable temperature range (ie, fit for use), and instructions will be provided to the subject on the correct storage and use of IP. Sharps containers for disposal of used IP syringes will be provided as well. Subjects will be asked to return unused IP, if any, at the completion of study participation, or immediately for DCTS subjects. The site will retain all unused IP until returned to the Sponsor or destroyed per IP Sponsor's instructions. The study site will maintain an accurate record of all IP allocations, shipments, and returns in a drug accountability log.

7.6 Treatment Compliance

Administration of IP will be conducted by study staff **or subject (refer to Table 7-1)** on scheduled visits. Subjects enrolled by the DCTS will be permitted to self-inject the IP in PFS at their own physical location (eg, home) under observation from the investigator/member of the study team via videoconference, after being trained on day 1 by the qualified study personnel on self-injections. Each injection will be documented.

Noncompliance is to be documented in the medical file/source documentation and will be reflected in the electronic CRF. Noncompliant subjects are to be re-educated on the importance of adhering to the IP administration schedule and reminded that repeated cycles of noncompliance could be a reason for discontinuation of study treatment.

7.7 Treatment of Overdose

Overdose with this product has not been reported. No specific antidote exists. In the case of an overdose, the subject should be treated symptomatically, and supportive measures implemented as necessary.

7.8 Prior and Concomitant Treatment

7.8.1 Prior Treatment

For prior migraine preventive medications, ending 2 months prior to start of baseline, therapy name, indication, dose, unit, frequency, start and stop dates will be collected in the prior migraine preventive medication CRF.

For all other prior therapies that were being taken/used within 120 days prior to screening through the signing of the informed consent, therapy name, start and stop dates will be collected in the concomitant medication CRF.

7.8.2 Concomitant Treatment

Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in Section 7.1.7.

Concomitant therapies are to be collected from signing of the informed consent through the end-of-study visit.

8. Discontinuation Criteria

Subjects have the right to withdraw from IP and/or other protocol-required therapies, protocol procedures, or the study as a whole at any time and for any reason without prejudice to their future medical care by the physician or at the institution.

The investigator and/or sponsor can decide to withdraw subject(s) from IP, device, and/or other protocol-required therapies, protocol procedures, or the study as a whole at any time prior to study completion for the reasons listed in Sections 8.1, 8.2.1, and 8.2.2.

8.1 Discontinuation of Study Treatment

Subjects (or a legally acceptable representative) can decline to continue receiving IP and/or other protocol-required therapies or procedures at any time during the study but continue participation in the study. If this occurs, the investigator is to discuss with the subject the appropriate processes for discontinuation from IP or other protocol-required therapies and must discuss with the subject the possibilities for continuation of the Schedule of Activities (see Section 2.2) including different options of follow-up (eg, in person, by phone/mail, through family/friends, in correspondence/communication with other treating physicians, from the review of medical records) and collection of data, including endpoints, adverse events, and device-related events, as applicable and must document this decision in the subject's medical records/source documentation. Subjects who have discontinued IP and/or other protocol-required therapies or procedures should not be automatically removed from the study. Whenever safe and feasible, it is imperative that subjects remain on-study to ensure safety surveillance and/or collection of outcome data.

Subjects may be eligible for continued treatment with Amgen IP(s) and/or other protocol-required therapies by a separate protocol or as provided for by the local country's regulatory mechanism, based on parameters consistent with Section 12.3.

Reasons for removal from protocol-required IP(s) or procedural assessments include any of the following:

- decision by sponsor
- lost to follow-up
- death
- ineligibility determined
- protocol deviation
- non-compliance
- adverse event
- subject request
- pregnancy

8.2 Discontinuation From the Study

Withdrawal of consent for a study means that the subject does not wish to receive further protocol-required therapies or procedures, and the subject does not wish to or is unable to continue further study participation. Subject data up to withdrawal of consent will be included in the analysis of the study, and where permitted, publicly available data can be included after withdrawal of consent. The investigator is to discuss with the subject appropriate procedures for withdrawal from the study and must document the subject's decision to withdraw in the subject's medical records/source documentation.

If a subject withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must notify Amgen accordingly (see Section 12.6 for further details). Refer to the Schedule of Activities (Table 2-1) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

8.2.1 Reasons for Removal From Washout, Run-in or Invasive Procedures

Not applicable to this study.

8.2.2 Reasons for Removal From Study

Reasons for removal of a subject from the study are:

- decision by sponsor
- withdrawal of consent from study
- death
- lost to follow-up

8.3 Lost to Follow-up

A subject will be considered lost to follow-up if he or she repeatedly fails to attend scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a subject fails to attend a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or is able to continue in the study.
- In cases in which the subject is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts are to be documented in the subject's medical record/source documentation.

- If the subject continues to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.
- For subjects who are lost to follow-up, the investigator can search publicly available records (where permitted) to ascertain survival status. This ensures that the data set(s) produced as an outcome of the study is/are as comprehensive as possible.

9. Study Assessments and Procedures

Study procedures and their time points are summarized in the Schedule of Activities (see Table 2-1).

As protocol waivers or exemptions are not allowed if an enrolled subject is subsequently determined to be ineligible for the study, this must be discussed with the sponsor immediately upon occurrence or awareness to determine if the subject is to continue or discontinue study treatment.

Adherence to the study design requirements, including those specified in the Schedule of Activities (Table 2-1), is essential and required for study conduct.

9.1 General Study Periods

9.1.1 Screening, Enrollment and/or Randomization

9.1.1.1 Screening Period

Informed consent must be obtained before any screening procedure or discontinuation of standard therapy for any disallowed therapy. After the subject has signed the informed consent form, the site will register the subject in the IRT and screen the subject in order to assess eligibility for participation. The screening period is up to 7 weeks, which consists of an initial screening up to 3 weeks (21 days) and a 4-week (28 days) baseline. The screening period starts when ICF is signed and dated by the subject and ends when the subject completes baseline and is randomized or screen failed.

All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, (see Section 6.6) as applicable.

If a subject has not met all eligibility criteria at the end of initial screening or baseline, the subject will be registered as a screen fail. Screen fail subjects may be rescreened one time if the condition(s) leading to ineligibility are transient and expected to improve or resolve in a timely manner.

Rescreen subjects must first be registered as screen failures in IRT and subsequently registered as rescreens. Once the subject is registered as a rescreen, a new screening

period will begin. Subjects will retain the same subject identification number assigned at the original screening. If the rescreening period begins more than 60 days after the original signing of the informed consent form, all screening procedures, including informed consent, must be repeated.

9.1.1.2 Baseline

The 4-week (28 days) baseline starts when the subject has met all initial (Part 1) eligibility criteria (refer to Section 6.1 and Section 6.2) and enters the baseline period. Baseline ends when the subject screen fails or does not meet all additional (Part 2) eligibility criteria (inclusion: 109 through 114; exclusion: 223 through 230), or when subject meets all eligibility criteria and is enrolled and randomized.

9.1.1.3 Randomization

Upon completion of baseline, subjects found to meet eligibility requirements will undergo randomization and be assigned a study treatment.

9.1.2 Treatment Period

Study visits will occur per the Schedule of Activities (Table 2-1). The date of the first dose of IP is defined as day 1 and must occur 28 to 35 days from the Day -28 visit. On-study visits after Day 1 may be completed within ± 3 days. All subsequent doses and study visits will be scheduled based on the day 1 date. Administration of protocol-required therapies is to be administered once every 4 weeks during each visit that it is required.

Subjects who discontinue IP are encouraged to remain in the study and complete all remaining procedures and study visits.

9.1.3 End-of-study

The end-of-study visit occurs at week 24 or 4 weeks after last dose of IP for subjects who discontinue study. All assessments will be performed at the end-of-study visit as per Schedule of Activities (Table 2-1).

9.2 Description of General Study Assessments and Procedures

The sections below provide a description of the individual study procedures for required time points.

9.2.1 General Assessments

9.2.1.1 Informed Consent

All subjects must sign and personally date the IRB/IEC approved informed consent before any study-specific procedures are performed.

Individuals recruited to the study as part of the DCTS will be provide electronic consent for their participation. A secure link to the web portal will be sent via email. Upon first access, the potential subject will receive a prompt to change the temporarily assigned password; the informed consent materials will then be presented through an electronic rendition of the IRB-approved consent document(s). Individuals will be able to review the consent document(s) and discuss the study with the investigator and/or designated study team member by telephone or videoconference, who will answer questions about the study and assess the individual's understanding.

Individuals who agree to take part in the study will provide their handwritten signature digitally executed to an electronic record using a computer mouse, touchscreen, or stylus on a computer or a tablet (depending on the capability of their web browser) in the designated signature block. The study team member administering the consent will countersign in the same manner. A copy of the fully executed consent documents will be provided to the subject, and the informed consent process will be documented and maintained as part of source documentation in the DCTS software.

9.2.1.2 Demographics

Demographic data collection including sex, age, race, and ethnicity will be collected in order to study their possible association with subject safety and treatment effectiveness.

9.2.1.3 Medical History

The Investigator or designee will collect a complete medical (including gastrointestinal- and cardiovascular-related history), psychiatric, and surgical history that started or was ongoing within 120 days prior to screening. Medical history will include information on the subject's concurrent medical conditions. Record all findings on the medical history CRF. In addition to the medical history above, neurological medical history must date back to the original diagnosis. The current severity will be collected for each condition that has not resolved.

Targeted medical history is to be recorded in the neurologic medical history CRF, cardiovascular medical history CRF, **gastrointestinal medical history CRF,** and headache and migraine frequency medical history CRF.

9.2.1.4 Physical Measurements

Height (in centimeters) and weight (in kilograms) should be measured without shoes.

9.2.1.5 Substance Abuse History

Obtain a detailed history of prior and/or concurrent use of alcohol, opioids/opioid-containing and butalbital/ butalbital-containing medications, prescription medication, recreational drugs, and any other psychoactive substance taken in the past 12 months (ie, stimulants and depressors such as ritalin, benzodiazepines, etc).

Obtain information about any prior history of diagnosed substance-related disorders.

9.2.2 Efficacy Assessments

9.2.2.1 Clinical Outcome Assessments and Electronic Diaries (eDiaries)

The clinical outcome assessments (COAs) will be collected by subjects using a handheld device with the eDiary. The eDiary will collect the following COAs daily at the subject's own physical location (eg, home):

- Date and time of start of headache (ie, migraine or nonmigraine headache)
- Date and time of end of each headache
- Worst pain severity per headache day
- Pain features (eg, 1-sided, throbbing, worsens, with exercise/physical activity)
- Symptoms (eg, aura, nausea, vomiting, photophobia, phonophobia)
- Use of acute medications (medication name/type [from pre-entered list], date of dosing)

Study site staff will assign and provide an eDiary to the subject at the baseline (day -28) visit (after confirming the subject's eligibility to enter the baseline period). The study site staff will train the subject on how to use the eDiary (eg, turning on/off, charging, navigating screens, transmitting data, contacting the help desk for technical assistance) and complete the questions. The subject will be instructed to interact with the eDiary every day and to have the eDiary during every study visit. At the day 1 visit prior to randomization, the investigator will use the subject's eDiary to review all data entered during baseline and confirm the relevant inclusion and exclusion criteria (inclusion: 109 through 114; exclusion: 223 through 230).

The handheld device, which will include the eDiary, will also be used for the completion of the following patient-reported outcome measures:

- Modified MIDAS
- WPAI
- MFIQ
- PHQ-9

- GAD-7
- PSQI
- ESS
- Patient satisfaction at work, at assessment time points during study visits

Completion of the following patient-reported outcome measure is not collected via the subject's handheld device, but is required to be assessed per protocol:

- PVT (Note: Subjects enrolled as part of the DCTS will not complete this assessment.)

9.2.2.1.1 Migraine Disability Assessment (MIDAS)

The MIDAS Questionnaire is a 5-item self-administered questionnaire that sums the number of productive days lost in 2 settings: the workplace and the home. The MIDAS also assesses disability in family, social, and leisure activities. The MIDAS score is the sum of missed days due to a headache from paid work, housework, and non-work (family, social, leisure) activities; and days at paid work or housework where productivity was reduced by at least half. The score is categorized into 4 severity grades: grade I = 0 to 5 (defined as minimal or infrequent disability), grade II = 6 to 10 (mild or infrequent disability), grade III = 11 to 20 (moderate disability), and grade IV = 21 and over (severe disability). The recall period for MIDAS is the past 3 months; the modified MIDAS has a 1-month recall period. Within the full MIDAS, two other questions (A and B) are not scored, but were designed to provide the physician with clinically relevant information on headache frequency and pain intensity.

9.2.2.1.2 Work Productivity and Activity Impairment (WPAI) Questionnaire

In the WPAI-Migraine, subjects are asked 6 questions about work and activity impairment due to their migraine, including hours worked and hours missed in the last 7 days. WPAI scores are based on 1-item (presenteeism, activity impairment), 2-items (absenteeism), and multiple items (overall work productivity); a score cannot be calculated if there is a missing response to the corresponding item. The questionnaire will be collected weekly.

9.2.2.1.3 Migraine Functional Impact Questionnaire (MFIQ)

The MFIQ is a self-administered 26-item instrument measuring the impact of migraine on broader functioning (ie, Physical, Usual Activities, Social, and Emotional). It has 4 domains: Impact on Physical Functioning (5 items), Impact on Usual Activities (10 items), Impact on Social Functioning (5 items), and Impact on Emotional Functioning (5 items). In addition, there is 1 stand-alone global item assessing the overall impact on

usual activities. Subjects respond to items using a 5-point scale assigned scores from 1 to 5, with 5 representing the greatest burden. The scores are calculated as the sum of the item responses and the sum is rescaled to a 0 to 100 scale, with higher scores representing greater burden. The recall period is the past 7 days.

9.2.2.1.4 Patient Health Questionnaire (PHQ-9)

The Patient Health Questionnaire (PHQ) is a 9-question, self-administered instrument for screening, diagnosing, monitoring, and measuring the severity of depression. It incorporates Diagnostic and Statistical Manual (of Mental Disorders) fourth edition (DSM-IV) depression diagnostic criteria with other leading major depressive symptoms into a brief self-report tool. The tool rates the frequency of the symptoms which factors into the scoring severity index. PHQ-9 scores each of the 9 DSM-IV criteria as "0" (not at all) to "3" (nearly every day). The score is calculated as the sum of the item responses and corresponds to one of the 5 severity categories:
Minimal or None = 0 to 4, Mild = 5 to 9, Moderate = 10 to 14,
Moderately Severe = 15 to 19, and Severe = 20 to 27.

Question 9 on the PHQ-9 screens for the presence and duration of suicide ideation.

9.2.2.1.5 Generalized Anxiety Disorder 7-item Scale Questionnaire (GAD-7)

The GAD-7 is a self-administered 7-item instrument that uses some of the Diagnostic and Statistical Manual (of Mental Disorders) fifth edition (DSM-V) criteria for general anxiety disorder (GAD) to identify probable cases of GAD along with measuring anxiety symptom severity. Responders are asked to rate the frequency of anxiety symptoms in the last 2 weeks on a Likert scale ranging from 0 (not at all) to 3 (nearly every day). Items are summed to provide a total score. Score interpretation is as follows:
1 to 4 minimal symptoms, 5 to 9 mild symptoms, 10 to 14 moderate symptoms, and 15 to 21 severe symptoms. Changes of 5 points or more are clinically meaningful.

9.2.2.1.6 Pittsburgh Sleep Quality Index (PSQI)

The PSQI is a self-reported questionnaire that assesses sleep quality over a 1-month time interval. The measure consists of 19 individual items, creating 7 components that produce 1 global score. The 7 components are subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction.

9.2.2.1.7 Epworth Sleepiness Scale (ESS)

The ESS is a self-administered questionnaire with 8 questions designed to assess daytime sleepiness. Respondents are asked to rate, on a 4-point scale (0 to 3), their usual chances of dozing off or falling asleep while engaged in 8 different activities. Most people engage in those activities at least occasionally, although not necessarily every day. The ESS score (the sum of 8 item scores, 0 to 3) can range from 0 to 24 with higher ESS scores indicating higher average sleep propensity (ASP) in daily life, or "daytime sleepiness". Score interpretation is as follows: 0 to 5 Lower Normal Daytime Sleepiness, 6 to 10 Higher Normal Daytime Sleepiness, 11 to 12 Mild Excessive Daytime Sleepiness, 13 to 15 Moderate Excessive Daytime Sleepiness, and 16 to 24 Severe Excessive Daytime Sleepiness.

9.2.2.1.8 Patient Satisfaction at Work

To better understand impact of depression, anxiety, sleepiness, and inability to concentrate on work productivity, subjects will be asked to complete the following questions via the handheld device:

- How much does your depressed mood, as a result of your migraines, impact your ability to function at work? Scale, 0 = no impact and 10 = severely impacts
- How much does your anxiety, as a result of your migraines, impact your ability to function at work? Scale, 0 = no impact and 10 = severely impacts
- How much does your sleepiness, as a result of your migraines, impact your ability to function at work? Scale, 0 = no impact and 10 = severely impacts
- How much does your inability to concentrate, as a result of your migraines, impact your ability to function at work? Scale, 0 = no impact and 10 = severely impacts
- How would you rate your overall satisfaction with your productivity at work? Scale, 0 = as dissatisfied as you can imagine and 10 = as satisfied as you can imagine

These questions are not part of a validated questionnaire and will be scored individually. The recall period is the past month.

9.2.2.1.9 Health Resource Utilization Questionnaire

The questionnaire is designed to collect data on HRU. Specifically, the aim is to capture frequency of migraine-related hospitalizations and outpatient visits including emergency department visits, urgent care visits, and other clinical visits. The recall period for the HRU questionnaire is 24 weeks, and the HRU questionnaire will be administered on day 1, and week 24 of the DBTP. The questionnaire assessed at the early termination

visit before week 24 should only include HRU recalled since the previous assessment at day 1 to avoid collecting duplicate information.

HRU questionnaire is an investigator-reported outcome collected through subject interview and/or available medical records at study visits. The HRU data will be entered in the HRU CRF.

9.2.2.1.10 Psychomotor Vigilance Task (PVT)

Psychomotor Vigilance Task is a sustained-attention, reaction-timed task that measures the speed with which a subject responds to a visual stimulus. The visual stimulus is a timer inside a rectangle against a solid background. The test is administered on a tablet, and once initiated, the subject responds by touching the bottom of the screen as soon as the numbers appear. The numbers are then cleared from the screen, another timer appears, and the subject touches the bottom of the screen to respond as previously done. Subject's reaction of touching the screen stops the timer, and the elapsed time from activation to deactivation, measured in milliseconds, is recorded. Mean reaction time, reciprocal mean reaction time, number of lapses and errors will be calculated from the individual elapsed time recordings during the 10-minute session. Subjects will be allowed to have a practice session to become familiar with the test.

Subjects enrolled as part of the DCTS will not complete this assessment.

9.2.2.2 Wearable Device

The wearable device is a watch-like accelerometer worn on the wrist for monitoring physical activity and sleep. The device records movements and communicates the data to a computer. Subjects are required to continuously wear the device every day except when recharging. Subjects whose medical history or professional activity is deemed to contraindicate or be incompatible with a compliant wearable device use may be made exempt from this requirement as per Amgen's medical monitor discretion upon consultation. Amgen must be consulted about the appropriateness of such exemption during screening.

9.2.3 Safety Assessments

Planned time points for all safety assessments are listed in the Schedule of Activities see (Table 2-1).

9.2.3.1 Adverse Events

9.2.3.1.1 Time Period and Frequency for Collecting and Reporting Safety Event Information

9.2.3.1.1.1 Adverse Events

The adverse event grading scale to be used for this study will be the Common Terminology Criteria for Adverse Events (CTCAE) and is described in Section 12.4.

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur after the first dose of IP through the end-of-study are reported using the Event CRF.

9.2.3.1.1.2 Serious Adverse Events

The investigator is responsible for ensuring that all serious adverse events observed by the investigator or reported by the subject that occur after signing of the informed consent through the end-of-study are reported using the Event CRF.

All serious adverse events will be collected, recorded and reported to the sponsor or designee within 24 hours, as indicated in Section 12.4. The investigator will submit any updated serious adverse event data to the sponsor within 24 hours of it being available.

The criteria for grade 4 in the CTCAE grading scale differs from the regulatory criteria for serious adverse events. It is left to the investigator's judgment to report these grade 4 abnormalities as serious adverse events.

9.2.3.1.1.3 Serious Adverse Events After the Protocol-required Reporting Period

There is no requirement to monitor study subjects for serious adverse events following the protocol-required reporting period or after end-of-study. However, these serious adverse events can be reported to Amgen. Per local requirements in some countries, investigators are required to report serious adverse events that they become aware of after end-of-study. If serious adverse events are reported, the investigator is to report them to Amgen within 24 hours following the investigator's knowledge of the event.

Serious adverse events reported outside of the protocol-required reporting period will be captured within the safety database as clinical trial cases and handled accordingly based on relationship to IP.

The method of recording, evaluating, and assessing causality of adverse events, adverse device effects, and serious adverse events and the procedures for completing and transmitting serious adverse event reports are provided in Section 12.4.

9.2.3.1.2 Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting adverse events and/or serious adverse events. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about adverse event occurrence.

For subjects enrolled as part of the DCTS, AEs are first reported to the investigator/study team or are identified by the study team during interactions with the subjects either via telephone or videoconferencing encounters. Additionally, AEs may be identified from lab reports or other records.

The investigator evaluates a potential event using information provided by the subject to determine if it meets the definition of an AE or an SAE. A course of action is prescribed if necessary and documentation is recorded in the DCTS software as source documentation. The appropriate medical intervention, therapeutic intervention, and/or support measures are instituted as necessary (ie, rescue medication administered, 911 called, emergency services utilized, mobile study personnel sent to subject's home). Follow-up and assessment of the AE/SAE until stabilized or resolved is completed per protocol (see Section 9.2.3.1.3 below).

Provision of study-issued smartphone allows subjects to contact the study team to report potential AEs at any time. Subjects can also request timely secure video or telephone conference with the investigator and/or designated members of the study team.

9.2.3.1.3 Follow-up of Adverse Events and Serious Adverse Events

After the initial adverse event/serious adverse event report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All adverse events and serious adverse events will be followed until resolution, stabilization, until the event is otherwise explained, or the subject is lost to follow-up (as defined in Section 8.3). Further information on follow-up procedures is given in Section 12.4.

All new information for previously reported serious adverse events must be sent to Amgen within 24 hours following knowledge of the new information. If specifically requested, the investigator may need to provide additional follow-up information, such as discharge summaries, medical records, or extracts from the medical records. Information provided about the serious adverse event must be consistent with that recorded on the Event CRF.

9.2.3.1.4 Regulatory Reporting Requirements for Serious Adverse Events

If subject is permanently withdrawn from protocol-required therapies because of a serious adverse event, this information must be submitted to Amgen.

Prompt notification by the investigator to the sponsor of serious adverse events is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a study treatment under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, and investigators.

Individual safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an individual safety report describing a serious adverse event or other specific safety information (eg, summary or listing of serious adverse events) from the sponsor will file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

To comply with worldwide reporting regulations for serious adverse events, the treatment assignment of subjects who develop serious, unexpected, and related adverse events may be unblinded by Amgen before submission to regulatory authorities. Aggregate analyses may also be unblinded by the Safety Assessment Team as appropriate. Investigators will receive notification of related serious adverse events reports sent to regulatory authorities in accordance with local requirements.

9.2.3.1.5 Pregnancy and Lactation

Details of all pregnancies and/or lactation in female subjects will be collected after the start of study treatment and through 16 weeks after last dose of IP.

If a pregnancy is reported, the investigator is to inform Amgen within 24 hours of learning of the pregnancy and/or lactation and is to follow the procedures outlined in Section 12.5. Amgen Global Patient Safety will follow-up with the investigator regarding additional information that may be requested.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered serious adverse events.

Further details regarding pregnancy and lactation are provided in Section 12.5.

9.2.3.1.6 Adverse Device Effects

In order to fulfill regulatory reporting obligations worldwide, the investigator is responsible for the detection and documentation of any adverse device effects that occur during the study with such devices.

An adverse device effect is any adverse event related to the use of a combination product or medical device. Adverse device effects include adverse events resulting from insufficient or inadequate instructions for use, adverse events resulting from any malfunction of the device, or adverse events resulting from use error or from intentional misuse of the device.

All adverse device effects are to be reported as adverse events following the same reporting periods and procedures.

Product complaints are described in Section 7.1.6.

Further details regarding adverse device effects can be found in Section 12.4.

9.2.3.1.7 Safety Monitoring Plan

Subject safety will be routinely monitored as defined in Amgen's safety surveillance and signal management processes.

9.2.4 Clinical Laboratory Assessments

Refer to Section 12.2 for the list of clinical laboratory tests to be performed and to the Schedule of Activities (Table 2-1) for the timing and frequency.

The investigator is responsible for reviewing laboratory test results and recording any clinically relevant changes occurring during the study in the Event CRF.

All protocol-required laboratory assessments, as defined in Section 12.2, must be conducted in accordance with the laboratory manual and the Schedule of Activities (Table 2-1).

Subjects enrolled as part of the DCTS may be requested to have their blood sample collected by an in-home phlebotomist with the exception of urine pregnancy test and urine drug testing, which may be self-collected.

9.2.4.1 Pregnancy Testing

A urine pregnancy test should be completed for females of childbearing potential as per the Schedule of Activities (Table 2-1).

Note: Females who have undergone a bilateral tubal ligation/occlusion should have pregnancy testing per protocol requirements. (If a female subject, or the partner of a male subject, becomes pregnant it must be reported on the Pregnancy Notification Worksheet, see Figure 12-2). Refer to Section 12.5 for contraceptive requirements.

Additional pregnancy testing should be performed at monthly intervals during treatment with protocol-required therapies and at the end-of-study visit.

Additional on-treatment pregnancy testing may be performed at the investigator's discretion or as required per local laws and regulations.

9.2.5 Pharmacogenetic Assessments

If the subject consents to the optional pharmacogenetic portion of this study, DNA analyses may be performed. These optional pharmacogenetic analyses focus on inherited genetic variations to evaluate their possible correlation to the disease and/or responsiveness to the therapies used in this study. The goals of the optional studies include the use of genetic markers to help in the investigation of migraines and/or to identify subjects who may have positive or negative response to AMG 334. No additional samples are collected for this part of the study. For subjects who consent to this/these analysis/analyses, DNA may be extracted from the cell pellet collected in the plasma tube used for the biomarker development sample.

The final disposition of samples will be described in Section 12.6.

9.2.6 Biomarkers

Biomarkers are objectively measured and evaluated indicators of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.

9.2.6.1 Biomarker Development/Future Research

Biomarker Development refers to using samples collected for Biomarker Discovery for future research after the study ends.

Biomarker development can be useful in developing markers to identify disease subtypes, guide therapy, and/or predict disease severity.

If consent is provided by subjects, biomarker discovery samples collected at the time points specified in the Schedule of Activities will be retained for future biomarker development as described in Section 12.6. No additional samples will be collected for biomarker development/future research.

Amgen or another third-party manufacturer may attempt to develop test(s) designed to identify subjects most likely to respond positively or negatively to AMG 334 to investigate and further understand migraines.

9.2.7 Health Economics OR Medical Resource Utilization and Health Economics

Health resource utilization data, associated with migraine-related medical encounters, will be collected in the CRF by the investigator and study-site personnel for all subjects throughout the study. Protocol-mandated procedures, tests, and encounters are excluded.

The data collected may be used to conduct exploratory economic analyses and will include:

- number of medical care encounters, including surgeries, and other selected procedures (inpatient and outpatient)
- duration of hospitalization (total days or length of stay)
- outpatient medical encounters (including physician or emergency room visits, and urgent care visits).

10. Statistical Considerations

10.1 Sample Size Determination

The total sample size of 240 subjects (120 subjects per treatment group) enrolled from traditional sites will provide at least a 94% power for the primary efficacy hypothesis. The statistical power for secondary efficacy hypotheses ranges from 88% to 99%. This sample size is not inflated for dropouts since subjects who drop out early during the 6-month DBTP are likely to have at least 1 post-baseline measurement and therefore will still be included in the analysis based on the primary estimand utilizing a repeated measures linear mixed model approach. Table 10-1 provides sample size assumptions and resulting statistical power for each hypothesis.

Table 10-1. Sample Size Assumptions and Statistical Power for Traditional Sites

Hypothesis	Assumed Treatment Effect (Erenumab – Placebo)	Assumed Common Standard Deviation	Power for Sample Size of 240 Subjects
Primary: modified MIDAS total score	-20	43	94%
Secondary:			
• MMD	-2.0	3.4	> 99%
• Work productivity impairment (WPAI)	-10.0	23.1	91%
• MFIQ physical function	-7.6	16.2	95%
• MFIQ usual activities	-6.1	14.9	88%
• MFIQ social function	-6.8	15.6	91%

MFIQ = Migraine Functional Impact Questionnaire; MIDAS = Migraine Disability Assessment; MMD = monthly migraine days; WPAI = Work Productivity and Activity Impairment.

Note: All power calculations are based on a 2-sided significance level of 0.05 and not adjusted to reflect the sequential testing procedure. The assumed treatment effects and common standard deviations for modified MIDAS, MMD, and MFIQ hypotheses are derived from a subset of subjects in erenumab Study 20120296 satisfying the key entry criteria of the current study. The assumed treatment effect and common standard deviation for the work impairment hypothesis is derived from the LIBERTY study.

In addition, a total sample size of 100 subjects (50 per treatment group) will be enrolled as part of the DCTS for pilot purposes.

10.2 Analysis Sets, Subgroups, and Covariates

10.2.1 Analysis Sets

All analyses will be performed by the traditional sites separately from DCTS. Therefore, respective analysis sets will be defined for traditional sites and DCTS.

10.2.1.1 Full Analysis Set

The respective full analysis set (FAS) consists of all subjects who were randomized in the study through traditional study sites or DCTS. Analysis of disposition, demographic and baseline characteristics, and important protocol deviations will utilize the respective FAS.

10.2.1.2 Efficacy Analysis Set

The respective efficacy analysis set (EAS) consists of a subset of subjects from traditional study sites or DCTS who receive at least 1 dose of IP and have a baseline value and at least 1 post baseline value for the endpoint of interest. Subjects will be analyzed according to their randomized treatment, regardless of the treatment received. Primary analysis of the efficacy endpoints will utilize the respective EAS.

10.2.1.3 Safety Analysis Set

The respective safety analysis set (SAS) will consist of all randomized subjects from traditional study sites or DCTS who received at least 1 dose of IP. Subjects will be analyzed according to the randomized treatment unless a subject has received the incorrect **treatment** during the entire DBTP. Analysis for safety endpoints and summary of IP administration will utilize the respective SAS.

10.2.2 Covariates

All model-adjusted analyses of efficacy endpoints will include the corresponding baseline value for the endpoint being analyzed.

10.2.3 Subgroups

The primary and secondary endpoints will be summarized in the subgroups defined by number of prior treatment failures (1, 2, and 3 or more treatment failures) for the traditional sites only.

10.2.4 Handling of Missing and Incomplete Data

Subjects may miss specific data points for a variety of reasons. In general, data could be missing due to a subject's early withdrawal from the study, a missed visit, or inability to evaluate an endpoint at a time point. For this study, efficacy endpoints will be collected via eDiary and subjects could miss entering several days of data in each monthly interval. The general procedures outlined below describe what will be done for missing data in efficacy.

For the endpoints derived from daily, if at least 14 days of eDiary are collected in the monthly interval, then the monthly frequency measurements (eg, migraine days) will be prorated based on the number of days with available information.

Missing items in each COA questionnaire will be handled based on the scoring algorithm for each COA.

Missing data after above methods will either be handled by the linear mixed effects model as the primary analysis method or the sensitivity analysis method detailed in Section 10.4.2.2.

Missing data in safety data will not be imputed.

10.3 Adaptive Design

Not applicable.

10.4 Statistical Analyses

The statistical analysis plan (SAP) will be developed and finalized before database lock. Below is a summary of the timing and methods for the planned statistical analyses. To preserve study integrity, the final analysis will be conducted and reported following the end-of-study, as defined in Section 5.3.1.

10.4.1 Planned Analyses

Primary Analysis

The primary analysis (or final analysis since there is only one milestone analysis for this study) will occur after all subjects have completed their week 24 visit (or discontinued from the study). The DBTP treatment assignment will be unblinded and all efficacy and safety analyses will be conducted and reported by the DBTP treatment group.

10.4.2 Methods of Analyses

10.4.2.1 General Considerations

All analyses will be conducted separately for subjects enrolled from traditional sites and subjects from DCTS. Formal statistical hypothesis testing for the primary and secondary endpoints will be performed for subjects enrolled from traditional sites only. Subject characteristics for both traditional sites and DCTS will be summarized descriptively.

Summary statistics by each treatment group will be tabulated at each assessment time point if applicable. For continuous endpoints, the descriptive statistics include: number of observations, means, medians, standard deviations, standard errors, first and third quartiles, minimums and maximums, and 2-sided 95% CIs of the means (CIs will be provided for efficacy endpoints only). For categorical endpoints, the summaries will contain the number and percentage of subjects in each category.

The primary analysis method utilizing a repeated measures linear mixed effects model will include all observed data regardless of treatment adherence.

A sequential testing procedure will be used to maintain the family-wise type 1 error $\alpha = 0.05$ between the primary and secondary endpoints following the order of modified MIDAS, MMD, WPAI, MFIQ physical function, MFIQ usual activity, and MFIQ social function endpoints. An endpoint will only be tested if the endpoint tested in the previous step is statistically significant at 2-sided significance level of 0.05.

10.4.2.2 Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary	Under the assumption of missing at random (MAR), the primary endpoint will be analyzed using a linear mixed effects model including treatment group, baseline value, scheduled visit, and the interaction of treatment group with scheduled visit, without any imputation for missing data. Multiple imputation (MI) with the assumption of missing not at random (MNAR) will be used as a sensitivity analysis to handle missing data at each assessment time point**,** using the analysis of covariance (ANCOVA) model including treatment group and baseline value.
Secondary	Under the assumption of MAR, the secondary endpoints will be analyzed using a linear mixed effects model including treatment group, baseline value, scheduled visit, and the interaction of treatment group with scheduled visit, without any imputation for missing data. MI with the assumption of MNAR will be used as a sensitivity analysis to handle missing data at each assessment time point**,** using the ANCOVA model including treatment group and baseline value.
Exploratory	Detailed primary analysis method for exploratory endpoints will be described in the SAP. No sensitivity analysis will be performed for exploratory endpoints.

10.4.2.2.1 Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) will be used to code all adverse events.

Subject incidence of all treatment-emergent adverse events will be tabulated by system organ class and preferred term or by preferred term in descending order of frequency. Tables of fatal adverse events, serious adverse events, adverse events leading to withdrawal from IP, adverse device effects, and significant treatment-emergent adverse events will also be provided. Subject incidence of device-related events, if applicable, will be tabulated by system organ class and preferred term.

10.4.2.2.2 Exposure to Investigational Product

The total length of IP exposure, the number of doses, and the proportion of subjects receiving each dose will be summarized using descriptive statistics.

10.4.2.2.3 Exposure to Concomitant Medication

Number and proportion of subjects receiving acute headache medications will be summarized by the medication category for each treatment group.

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12. Appendices

12.1 Appendix 1. List of Abbreviations and Definitions of Terms

Abbreviation or Term	Definition/Explanation
ACE	angiotensin-converting enzyme
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AMPP	American Migraine Prevalence and Prevention
ASP	average sleep propensity
AST	aspartate aminotransferase
ATA	American Telemedicine Association
CaMEO	Chronic Migraine Epidemiology and Outcomes
CFR	Code of Federal Regulations
CGRP	calcitonin gene-related peptide
CM	chronic migraine
COA	clinical outcome assessment
CRF	case report form
CRO	Contract Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
DBTP	double-blind treatment period
DCTS	decentralized clinical trial site
DILI	drug-induced liver injury
DSM-IV	Diagnostic and Statistical Manual (of Mental Disorders) fourth edition
DSM-V	Diagnostic and Statistical Manual (of Mental Disorders) fifth edition
EAS	efficacy analysis set
EDC	electronic data capture
eDiary	electronic diary
EM	episodic migraine
End-of-study for Individual Subject	defined as the last day that protocol-specified procedures are conducted for an individual subject
End-of-study (primary completion)	defined as the date when the last subject is assessed or receives an intervention for the final collection of data for the primary endpoint(s), whether the study concluded as planned in the protocol or was terminated early
End-of-study (end of trial), EOS	defined as the date when the last subject across all sites is assessed or receives an intervention for evaluation in the study (ie, last subject last visit), following any additional parts in the study (eg, long-term follow-up), as applicable
End of Treatment	defined as the last assessment for the protocol-specified treatment period of the study for an individual subject

Abbreviation or Term	Definition/Explanation
Enrollment	defined as the day a subject has met all Part 1 and Part 2 eligibility criteria and is enrolled and randomized into the study (subjects are randomized same day)
ESS	Epworth Sleepiness Scale
FSH	follicle stimulating hormone
FAS	full analysis set
GAD	generalized anxiety disorder
GAD-7	Generalized Anxiety Disorder 7-item Scale
GCP	Good Clinical Practice
Headache	a migraine or non-migraine headache
Headache day	Any calendar day in which the subject experiences a qualified headache (initial onset, continuation, or recurrence of the headache). A qualified headache is defined as: • a qualified migraine headache (including an aura-only event that is treated with acute migraine-specific medication) or • a qualified non-migraine headache, which is a headache that lasts ≥ 30 minutes and is not a qualified migraine headache or • a headache of any duration for which acute headache treatment is administered
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency
HIT-6	Headache Impact Test-6
HRT	hormone replacement therapy
HRU	Health Resource Utilization
ICH	International Council for Harmonisation
ICHD-III	International Classification of Headache Disorders, Third Edition
IEC	Independent Ethics Committee
IgG2	immunoglobulin G2
IHS	International Headache Society
INR	international normalized ratio
IP	investigational product
IPIM	Investigational Product Instruction Manual
IRB	Institutional Review Board
IRT	interactive response technology
IUD	intrauterine device
IUS	intrauterine hormonal-releasing system
LIBERTY	A Study Evaluating the Effectiveness of AMG 334 Injection in Preventing Migraines in Adults Having Failed Other Therapies
MAR	missing at random

Abbreviation or Term	Definition/Explanation
MFIQ	Migraine Functional Impact Questionnaire
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputation
Modified MIDAS	modified Migraine Disability Assessment
MIDAS	Migraine Disability Assessment
Migraine day	A migraine day is defined as any calendar day in which the subject experiences a qualified migraine headache (onset, continuation or recurrence of the migraine headache). A qualified migraine headache is defined as a migraine with or without aura lasting for ≥ 30 minutes, and meeting at least 1 of the following criteria (a and/or b): a. ≥ 2 of the following pain features: • Unilateral • Throbbing • Moderate to severe • Exacerbated with exercise/physical activity b. ≥ 1 of the following associated symptoms: • Nausea and/or vomiting • Phonophobia and photophobia If the subject took a migraine-specific medication (ie, triptan, or ergotamine) during aura or to treat headache on a calendar day, then it will be counted as a migraine day regardless of the duration and pain features/associated symptoms.
MMD	monthly migraine days
MNAR	missing not at random
MPFID	Migraine Physical Function Impact Diary
NCT	National Clinical Trials
PFS	prefilled syringes
PHQ-9	Patient Health Questionnaire
PSQI	Pittsburgh Sleep Quality Index
PVT	Psychomotor Vigilance Task
Q4W	every 4 weeks
QM	once monthly
Randomization	defined as the day a subject has met all Part 1 and Part 2 eligibility criteria and is enrolled and randomized into the study (subjects are enrolled same day)
SAS	safety analysis set
SAP	statistical analysis plan
SC	subcutaneous(ly)

Abbreviation or Term	Definition/Explanation
Source Data	information from an original record or certified copy of the original record containing patient information for use in clinical research. The information may include, but is not limited to, clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies). (ICH Guideline [E6]). Examples of source data include Subject identification, Randomization identification, and Stratification Value.
STRIVE	Study to Evaluate the Efficacy and Safety of Erenumab in Migraine Prevention
Study Day 1	defined as the first day that protocol-specified IP(s)/protocol-required therapies is/are administered to the subject
SUSAR	suspected unexpected serious adverse reaction
TBL	total bilirubin
ULN	upper limit of normal
US	United States
WPAI	Work Productivity and Activity Impairment Questionnaire

12.2 Appendix 2. Clinical Laboratory Tests

The tests detailed in Table 12-1 will be performed by the local laboratory. The tests performed by central laboratory are optional.

Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 12-1. Analyte Listing

Local Laboratory	(Optional) Central Laboratory
Urine pregnancy Urine drug testing	Biomarker development Pharmacogenetic assessment

12.3 Appendix 3. Study Governance Considerations

Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
- Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
- Applicable ICH laws and regulations

The protocol, protocol amendments, informed consent form, Investigator's Brochure, and other relevant documents (eg, subject recruitment advertisements) must be submitted to an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) by the investigator and reviewed and approved by the IRB/IEC. A copy of the written approval of the protocol and informed consent form must be received by Amgen before recruitment of subjects into the study and shipment of Amgen IP.

Amgen may amend the protocol at any time. The investigator must submit and, where necessary, obtain approval from the IRB/IEC for all subsequent protocol amendments and changes to the informed consent document. The investigator must send a copy of the approval letter from the IRB/IEC and amended protocol Investigator's Signature page to Amgen prior to implementation of the protocol amendment at their site.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Obtaining annual IRB/IEC approval/renewal throughout the duration of the study. Copies of the investigator's reports and the IRB/IEC continuance of approval must be sent to Amgen
- Notifying the IRB/IEC of serious adverse events occurring at the site, deviations from the protocol or other adverse event reports received from Amgen, in accordance with local procedures
- Overall conduct of the study at the site and adherence to requirements of Title 21 of the U.S. Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, and all other applicable local regulations

Recruitment Procedures

Site staff will identify potential subjects from their existing patient population or may seek referral patients through existing professional networks or other community sources such

as patient advocacy groups. Also, digital recruitment strategies may also be used. All patient facing materials must be reviewed/approved by the sponsor (Amgen Inc.) and the local IRB/IEC.

Informed Consent Process

An initial sample informed consent form is provided for the investigator to prepare the informed consent document to be used at his or her site. Updates to the sample informed consent form are to be communicated formally in writing from the Amgen Trial Manager to the investigator. The written informed consent form is to be prepared in the language(s) of the potential patient population.

The investigator or his/her delegated representative will explain to the subject, the aims, methods, anticipated benefits, and potential hazards of the study before any protocol-specific screening procedures or any IP(s) is/are administered, and answer all questions regarding the study.

Subjects must be informed that their participation is voluntary. Subjects will then be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study site.

The medical record/source documentation must include a statement that written informed consent was obtained before the subject was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the informed consent form.

The investigator is also responsible for asking the subject if the subject has a primary care physician and if the subject agrees to have his/her primary care physician informed of the subject's participation in the clinical study unless it is a local requirement. The investigator shall then inform the primary care physician. If the subject agrees to such notification, the investigator is to inform the subject's primary care physician of the subject's participation in the clinical study. If the subject does not have a primary care physician and the investigator will be acting in that capacity, the investigator is to document such in the subject's medical record.

The acquisition of informed consent is to be documented in the subject's medical records/source documentation, and the informed consent form is to be signed and personally dated by the subject and by the person who conducted the informed consent

discussion. Subject withdrawal of consent or discontinuation from study treatment and/or procedures must also be documented in the subject's medical records; refer to Section 8.

Subjects must be re-consented to the most current version of the informed consent form(s) during their participation in the study.

The original signed informed consent form is to be retained in accordance with institutional policy, and a copy of the informed consent form(s) must be provided to the subject.

The informed consent form will contain a separate section that addresses the use of remaining mandatory samples for optional future research. The investigator or authorized designee will explain to each subject the objectives of the future research. Subjects will be told that they are free to refuse to participate and may withdraw their specimens at any time and for any reason during the storage period. A separate signature will be required to document a subject's agreement to allow any remaining specimens to be used for future research. Subjects who decline to participate will not provide this separate signature.

Data Protection/Subject Confidentiality

The investigator must ensure that the subject's confidentiality is maintained for documents submitted to Amgen.

Subject will be assigned a unique identifier by the sponsor. Any subject records or datasets that are transferred to the sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.

On the Case Report Form (CRF) demographics page, in addition to the unique subject identification number, include the age at time of enrollment.

For serious adverse events reported to Amgen, subjects are to be identified by their unique subject identification number, initials (for faxed reports, in accordance with local laws and regulations), and age (in accordance with local laws and regulations).

Documents that are not submitted to Amgen (eg, signed informed consent forms) are to be kept in confidence by the investigator, except as described below.

In compliance with governmental regulations/ICH GCP Guidelines, it is required that the investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IRB/IEC direct access to review the subject's original

medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study.

The investigator is obligated to inform and obtain the consent of the subject to permit such individuals to have access to his/her study-related records, including personal information.

Publication Policy

To coordinate dissemination of data from this study, Amgen may facilitate the formation of a publication committee consisting of several investigators and appropriate Amgen staff, the governance and responsibilities of which are set forth in a Publication Charter. The committee is expected to solicit input and assistance from other investigators and to collaborate with authors and Amgen staff, as appropriate, as defined in the Publication Charter. Membership on the committee (both for investigators and Amgen staff) does not guarantee authorship. The criteria described below are to be met for every publication.

Authorship of any publications resulting from this study will be determined on the basis of the Uniform Requirement for Manuscripts Submitted to Biomedical Journals International Committee of Medical Journal Editors Recommendations for the Conduct of Reporting, Editing, and Publications of Scholarly Work in Medical Journals, which states: Authorship credit is to be based on: (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published; and (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Authors need to meet conditions 1, 2, 3, and 4.

When a large, multicenter group has conducted the work, the group is to identify the individuals who accept direct responsibility for the manuscript. These individuals must fully meet the criteria for authorship defined above. Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship. All persons designated as authors must qualify for authorship, and all those who qualify are to be listed. Each author must have participated sufficiently in the work to take public responsibility for appropriate portions of the content. All publications (eg, manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be

submitted to Amgen for review. The Clinical Trial Agreement among the institution, investigator, and Amgen will detail the procedures for, and timing of, Amgen's review of publications.

Investigator Signatory Obligations

Each clinical study report is to be signed by the investigator or, in the case of multicenter studies, the coordinating investigator.

The coordinating investigator, identified by Amgen, will be any or all of the following:

- A recognized expert in the therapeutic area
- An Investigator who provided significant contributions to either the design or interpretation of the study
- An Investigator contributing a high number of eligible subjects

Data Quality Assurance

All subject data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data, centrally or adjudicated data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

The sponsor or designee is responsible for the data management of this study including quality checking of the data.

Clinical monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements per the sponsor's monitoring plan.

The investigator agrees to cooperate with the clinical monitor to ensure that any problems detected in the course of these monitoring visits, including delays in completing CRFs, are resolved.

The Amgen representative(s) and regulatory authority inspectors are responsible for contacting and visiting the investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the clinical study (eg, CRFs and other pertinent data) provided that subject confidentiality is respected.

In accordance with ICH GCP and the sponsor's audit plans, this study may be selected for audit by representatives from Amgen's Global Research and Development Compliance and Audit function (or designees). Inspection of site facilities (eg, pharmacy, protocol-required therapy storage areas, laboratories) and review of study-related records will occur to evaluate the study conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements.

Retention of study documents will be governed by the Clinical Trial Agreement.

Case report forms (CRF) must be completed in English. TRADENAMES® (if used) for concomitant medications may be entered in the local language. Consult the country-specific language requirements.

All written information and other material to be used by subjects and investigative staff must use vocabulary and language that are clearly understood.

Source Documents

The investigator is to maintain a list of appropriately qualified persons to whom he/she has delegated study duties. All persons authorized to make entries and/or corrections on CRFs will be included on the Amgen Delegation of Authority Form.

Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the investigator's site. For DCTS, source documentation will be maintained in the DCTS software.

Source documents are original documents, data, and records from which the subject's CRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence. Source documents may also include data captured in the interactive response technology (IRT) (if used, such as subject ID and randomization number) and CRF entries if the CRF is the site of the original recording (ie, there is no other written or electronic record of data, such as paper questionnaires for a clinical outcome assessment [COA]).

Data reported on the CRF or entered in the electronic CRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

The Investigator and study staff are responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation, suitable for inspection at any time by representatives from Amgen and/or applicable regulatory authorities.
Elements to include:

- Subject files containing completed CRFs, informed consent forms, and subject identification list
- Study files containing the protocol with all amendments, Investigator's Brochure, copies of prestudy documentation, and all correspondence to and from the (IRB/IEC) and Amgen
- Investigational product-related correspondence including Proof of Receipts, IP Accountability Record(s), Return of IP for Destruction Form(s), Final IP Reconciliation Statement, as applicable
- Non-IP(s), and/or medical device(s) or combination product(s) documentation, as applicable

Retention of study documents will be governed by the Clinical Trial Agreement.

Study and Site Closure

Amgen or its designee may stop the study or study site participation in the study for medical, safety, regulatory, administrative, or other reasons consistent with applicable laws, regulations, and GCP.

Both Amgen and the Investigator reserve the right to terminate the Investigator's participation in the study according to the Clinical Trial Agreement. The investigator is to notify the IRB/IEC in writing of the study's completion or early termination and send a copy of the notification to Amgen.

Subjects may be eligible for continued treatment with Amgen IP(s) by an extension protocol or as provided for by the local country's regulatory mechanism. However, Amgen reserves the unilateral right, at its sole discretion, to determine whether to supply Amgen IP(s) and by what mechanism, after termination of the study and before the product(s) is/are available commercially.

Compensation

Any arrangements for compensation to subjects for injury or illness that arises in the study are described in the Compensation for Injury section of the Informed Consent that is available as a separate document.

12.4 Appendix 4. Safety Events: Definitions and Procedures for Recording, Evaluating, Follow-up and Reporting

Definition of Adverse Event

Adverse Event Definition
• An adverse event is any untoward medical occurrence in a clinical study subject irrespective of a causal relationship with the study treatment. • Note: An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a treatment, combination product, medical device or procedure.

Events Meeting the Adverse Event Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, electrocardiogram, radiological scans, vital signs measurements), including those that worsen from baseline, that are considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an adverse event/serious adverse event unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses are to be reported regardless of sequelae. • “Lack of efficacy” or “failure of expected pharmacological action” per se will not be reported as an adverse event or serious adverse event. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as adverse event or serious adverse event if they fulfill the definition of an adverse event or serious adverse event.

Events NOT Meeting the Adverse Event Definition
• Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the adverse event. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of Serious Adverse Event

A Serious Adverse Event is defined as any untoward medical occurrence that, meets at least 1 of the following serious criteria:
Results in death (fatal)
Immediately life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
Requires in-patient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are an adverse event. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the adverse event is to be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an adverse event.
Results in persistent or significant disability/incapacity The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
Is a congenital anomaly/birth defect
Other medically important serious event Medical or scientific judgment is to be exercised in deciding whether serious adverse event reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events are typically to be considered serious. Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Definition of Adverse Device Effect

The detection and documentation procedures for adverse device effects described in this protocol apply to all Amgen medical devices provided for use in the study (see Section 7.1.3 for the list of Amgen medical devices).

Adverse Device Effect Definition
An adverse device effect is any adverse event related to the use of a combination product or medical device. Adverse device effects include adverse events resulting from insufficient or inadequate instructions for use, adverse events resulting from any malfunction of the device, or adverse events resulting from use error or from intentional misuse of the device.

Recording Adverse Events and Serious Adverse Events

Adverse Event and Serious Adverse Event Recording
• When an adverse event or serious adverse event occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event. • The investigator will then record all relevant adverse event/serious adverse event information in the Event case report form (CRF). • The investigator must assign the following adverse event attributes: – Adverse event diagnosis or syndrome(s), if known (if not known, signs or symptoms); – Dates of onset and resolution (if resolved); – Severity (or toxicity defined below); – Assessment of relatedness to IP (erenumab or placebo), other protocol-required therapies, or Amgen medical devices (prefilled syringe [PFS]); and – Action taken. • If the severity of an adverse event changes from the date of onset to the date of resolution, record as a single event with the worst severity on the Event CRF. • It is not acceptable for the investigator to send photocopies of the subject's medical records to sponsor in lieu of completion of the Event CRF page. • If specifically requested, the investigator may need to provide additional follow-up information, such as discharge summaries, medical records, or extracts from the medical records. In this case, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records before submission to Amgen. • The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the adverse event/serious adverse event.

Evaluating Adverse Events and Serious Adverse Events

Assessment of Severity
The investigator will make an assessment of severity for each adverse event and serious adverse event reported during the study. The assessment of severity will be based on: The Common Terminology Criteria for Adverse Events, version **4.03** which is available at the following location: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

Assessment of Causality
• The investigator is obligated to assess the relationship between IP, device(s), and/or study-mandated procedure and each occurrence of each adverse event/serious adverse event. • Relatedness means that there are facts or reasons to support a relationship between IP and the event. • The investigator will use clinical judgment to determine the relationship. • Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated. • The investigator will also consult the Investigator's Brochure and/or Product Information, for marketed products, in his/her assessment. • For each adverse event/serious adverse event, the investigator must document in the medical notes that he/she has reviewed the adverse event/serious adverse event and has provided an assessment of causality. • There may be situations in which a serious adverse event has occurred and the investigator has minimal information to include in the initial report. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the serious adverse event data. • The investigator may change his/her opinion of causality in light of follow-up information and send a serious adverse event follow-up report with the updated causality assessment. • The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

Follow-up of Adverse Event and Serious Adverse Event
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Amgen to elucidate the nature and/or causality of the adverse event or serious adverse event as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. • If a subject is permanently withdrawn from protocol-required therapies because of a serious adverse event, this information must be submitted to Amgen. • If a subject dies during participation in the study or during a recognized follow-up period, the investigator will provide Amgen with a copy of any post-mortem findings including histopathology. • New or updated information will be recorded in the originally completed Event CRF. • The investigator will submit any updated serious adverse event data to Amgen within 24 hours of receipt of the information.

Reporting of Serious Adverse Event

Serious Adverse Event Reporting via Electronic Data Collection Tool
• The primary mechanism for reporting serious adverse event will be the electronic data capture (EDC) system via the Safety Report Form. • If the EDC system is unavailable for more than 24 hours, then the site will report the information to Amgen using an electronic Serious Adverse Contingency Report Form (see Figure 12-1) within 24 hours of the investigator's knowledge of the event. • The site will enter the serious adverse event data into the electronic system as soon as it becomes available. • After the study is completed at a given site, the EDC system will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new serious adverse event from a study subject or receives updated data on a previously reported serious adverse event after the EDC has been taken off-line, then the site can report this information on a paper Serious Adverse Event Report Form (see Figure 12-1).

Adverse Device Effects: Recording, Evaluating and Reporting

- Any adverse event resulting from an adverse device effect that occur during the study will be documented in the subject's medical records, in accordance with the investigator's normal clinical practice, and on the Event CRF page.
- It is very important that the investigator provides his/her assessment of causality (relationship to the medical device provided by Amgen) at the time of the initial report and describes any corrective or remedial actions taken to prevent recurrence of the incident.

Figure 12-1. Sample Electronic Serious Adverse Event Contingency Form

AMGEN
Study # 20180060
AMG 334

Electronic Serious Adverse Event Contingency Report Form
For Restricted Use

Reason for reporting this event via fax
The Clinical Trial Database (eg. Rave):
☐ Is not available due to internet outage at my site
☐ Is not yet available for this study
☐ Has been closed for this study

US: +888 814 8653

1. SITE INFORMATION

Site Number	Investigator	Country

Reporter	Phone Number	Fax Number
	( )	( )

2. SUBJECT INFORMATION

Subject ID Number	Age at event onset	Sex	Race	If applicable, provide End of Study date
		☐F ☐M		

If this is a follow-up to an event reported in the EDC system (eg, Rave), provide the adverse event term: _____
and start date: Day _____ Month _____ Year _____

3. SERIOUS ADVERSE EVENT

Provide the date the Investigator became aware of this information: Day Month Year

Serious Adverse Event diagnosis or syndrome If diagnosis is unknown, enter signs / symptoms and provide diagnosis, when known, in a follow-up report *List one event per line. If event is fatal, enter the cause of eeath. Entry of "death" is not acceptable, as this is an outcome.*	**Date Started** Day Month Year	**Date Ended** Day Month Year	Check only if event occurred before first dose of IP	**Is event serious?**	**If serious, enter Serious Criteria code** *(see codes below)*	**Relationship** Is there a reasonable possibility that theEvent may have been caused by IP or an Amgen device used to administer the IP? AMG 334 No✓ Yes✓ PFS No✓ Yes✓	**Outcome of Event** -Resolved -Not resolved -Fatal -Unknown	Check only if event is related to study procedure eg, biopsy
				☐Yes ☐No				
				☐Yes ☐No				
				☐Yes ☐No				

Serious Criteria: **01** Fatal; **02** Immediately life-threatening; **03** Required/prolonged hospitalization; **04** Persistent or significant disability /incapacity; **05** Congenital anomaly / birth defect; **06** Other medically important serious event

4. Was subject hospitalized or was a hospitalization prolonged due this event? ☐No ☐Yes If yes, please complete all of Section 4

Date Admitted Day Month Year	Date Discharged Day Month Year

5. Was IP/drug under study administered/taken prior to this event? ☐No ☐Yes If yes, please complete all of Section 5

IP/Amgen Device:		Date of Initial Dose Day Month Year	Prior to, or at time of Event: Date of Dose Day Month Year	Dose	Route	Frequency	**Action Taken with Product** 01 Still being Administered 02 Permanently discontinued 03 Withheld	**Lot # and Serial #**
<<IP/Device>>	☐ blinded ☐ open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown
<<IP/Device>>	☐ blinded ☐ open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown

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AMGEN Study # 20180060 AMG 334	Electronic Serious Adverse Event Contingency Report Form For Restricted Use

Site Number	Subject ID Number

6. CONCOMITANT MEDICATIONS (eg, chemotherapy) Any Medications? ☐ No ☐ Yes If yes, please complete:

Medication Name(s)	Start Date (Day Month Year)	Stop Date (Day Month Year)	Co-suspect No✓	Co-suspect Yes✓	Continuing No✓	Continuing Yes✓	Dose	Route	Freq.	Treatment Med No✓	Treatment Med Yes✓

7. RELEVANT MEDICAL HISTORY ***(include dates, allergies and any relevant prior therapy)***

8. RELEVANT LABORATORY VALUES ***(include baseline values)*** Any Relevant Laboratory values? ☐ No ☐ Yes If yes, please complete:

Date (Day Month Year) / Test / Unit											

9. OTHER RELEVANT TESTS ***(diagnostics and procedures)*** Any Other Relevant tests? ☐ No ☐ Yes If yes, please complete:

Date (Day Month Year)	Additional Tests	Results	Units

AMGEN Study # 20180060 AMG 334	Electronic Serious Adverse Event Contingency Report Form For Restricted Use

Site Number	Subject ID Number

10. CASE DESCRIPTION ***(Provide narrative details of events listed in section 3)*** Provide additional pages if necessary. For each event in section 3, where relationship=Yes, please provide rationale.

Signature of Investigator or Designee - *I confirm by signing this report that the information on this form, including seriousness and causality assessments, is being provided to Amgen by the investigator for this study, or by a Qualified Medical Person authorized by the investigator for this study.*	Title	Date

12.5 Appendix 5. Contraceptive Guidance and Collection of Pregnancy and Lactation Information

Study-specific contraception requirements for female of childbearing potential are outlined in Section 6.2.

Female subjects of childbearing potential must receive pregnancy prevention counseling and be advised of the risk to the fetus if they become pregnant during treatment and for an additional 16 weeks after the last dose of IP.

Definition of Females of Childbearing Potential

A female is considered fertile following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Females in the following categories are not considered female of childbearing potential:

- Premenopausal female with 1 of the following:
  - Documented hysterectomy;
  - Documented bilateral salpingectomy; or
  - Documented bilateral oophorectomy.

  Note: Site personnel documentation from the following sources is acceptable: 1) review of subject's medical records; 2) subject's medical examination; or 3) subject's medical history interview.
- Premenarchal female
- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
  - Females on HRT and whose menopausal status is in doubt will be required to use 1 of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Methods for Female Subjects

Acceptable Methods of Effective Contraception

- combined (estrogen and progestogen containing) or progestogen-only hormonal methods given via oral, intravaginal, transdermal, injectable, or implantable route
- intrauterine device (IUD)
- intrauterine hormonal-releasing system (IUS)

- bilateral tubal ligation/occlusion
- vasectomized partner (provided that partner is the sole sexual partner of the female subject of childbearing potential and that the vasectomized partner has received medical assessment of the surgical success)
- sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments; the reliability of sexual abstinence must be evaluated in relation to the duration of the trial and the preferred and usual lifestyle of the subject)
- male or female condom with or without spermicide
- cap, diaphragm or sponge with spermicide
- double-barrier method: the male uses a condom and the female may choose either a cap, diaphragm, or sponge with spermicide (a female condom is not an option due to the risk of tearing when both partners use a condom)

Unacceptable Methods of Birth Control for Female Subjects

Birth control methods that are considered unacceptable in clinical trials include:

- periodic abstinence (calendar, symptothermal, post-ovulation methods)
- withdrawal (coitus interruptus)
- spermicides only
- lactational amenorrhea method

Collection of Pregnancy Information

Female Subjects Who Become Pregnant

- Investigator will collect pregnancy information on any female subject who becomes pregnant while taking protocol-required therapies through 16 weeks after the last dose of IP.
- Information will be recorded on the Pregnancy Notification Worksheet (see Figure 12-2). The worksheet must be submitted to Amgen Global Patient Safety within 24 hours of learning of a subject's pregnancy. (Note: Sites are not required to provide any information on the Pregnancy Notification Worksheet that violates the country or regions local privacy laws).
- After obtaining the female subject's signed authorization for release of pregnancy and infant health information, the investigator will collect pregnancy and infant health information and complete the pregnancy questionnaire for any female subject who becomes pregnant while taking protocol-required therapies through 16 weeks of last dose of IP of the study drug. This information will be forwarded to Amgen Global Patient Safety. Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).
- Any termination of pregnancy will be reported to Amgen Global Patient Safety, regardless of fetal status (presence or absence of anomalies) or indication for procedure.

- While pregnancy itself is not considered to be an adverse event or serious adverse event, any pregnancy complication or report of a congenital anomaly or developmental delay, fetal death, or suspected adverse reactions in the neonate will be reported as an adverse event or serious adverse event. Note that an elective termination with no information on a fetal congenital malformation or maternal complication is generally not considered an adverse event, but still must be reported to Amgen as a pregnancy exposure case.
- If the outcome of the pregnancy meets a criterion for immediate classification as a serious adverse event (eg, female subject experiences a spontaneous abortion, stillbirth, or neonatal death or there is a fetal or neonatal congenital anomaly) the investigator will report the event as a serious adverse event.
- Any serious adverse event occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to Amgen Global Patient Safety as described in Section 12.4. While the investigator is not obligated to actively seek this information in former study subjects, he or she may learn of a serious adverse event through spontaneous reporting.
- Any female subject who becomes pregnant while participating will discontinue study treatment (see Section 8.1 for details).

Male Subjects With Partners Who Become Pregnant

- In the event a male subject fathers a child during treatment, and for an additional 16 weeks after discontinuing protocol-required therapies, the information will be recorded on the Pregnancy Notification Worksheet. The worksheet (see Figure 12-2) must be submitted to Amgen Global Patient Safety within 24 hours of the site's awareness of the pregnancy. (Note: Sites are not required to provide any information on the Pregnancy Notification Worksheet that violates the country or regions local privacy laws).
- The investigator will attempt to obtain a signed authorization for release of pregnancy and infant health information directly from the pregnant female partner to obtain additional pregnancy information.
- After obtaining the female partner's signed authorization for release of pregnancy and infant health information, the investigator will collect pregnancy outcome and infant health information on the pregnant partner and her baby and complete the pregnancy questionnaires. This information will be forwarded to Amgen Global Patient Safety.
- Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).
- Any termination of the pregnancy will be reported to Amgen Global Patient Safety regardless of fetal status (presence or absence of anomalies) or indication for procedure.

Collection of Lactation Information

- Investigator will collect lactation information on any female subject who breastfeeds while taking protocol-required therapies through 16 weeks after the last dose of IP.
- Information will be recorded on the Lactation Notification Worksheet (see below) and submitted to Amgen Global Patient Safety within 24 hours of the investigator's knowledge of event.

- Study treatment will be discontinued if female subject breastfeeds during the study as described in exclusion criterion 217.
- With the female subjects signed authorization for release of mother and infant health information, the investigator will collect mother and infant health information and complete the lactation questionnaire on any female subject who breastfeeds while taking protocol-required therapies through 16 weeks after the last dose of IP.

Figure 12-2. Pregnancy and Lactation Notification Worksheet

Amgen Proprietary - Confidential

AMGEN Pregnancy Notification Form

Report to Amgen at: USTO fax: +1-888-814-8653, Non-US fax: +44 (0)207-136-1046 or email (worldwide): svc-ags-in-us@amgen.com

1. Case Administrative Information

Protocol/Study Number: 20180060

Study Design: ☑ Interventional ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

2. Contact Information

Investigator Name _____ **Site #** _____

Phone (____)_____ **Fax** (____)_____ **Email** _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject Gender:** ☐ Female ☐ Male **Subject age (at onset):** ____ (in years)

4. Amgen Product Exposure

Amgen Product	Dose at time of conception	Frequency	Route	Start Date
				mm____/dd____/yyyy____

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm ____/dd____/yyyy____

Did the subject withdraw from the study? ☐ Yes ☐ No

5. Pregnancy Information

Pregnant female's last menstrual period (LMP) mm_____/ dd_____/ yyyy_____ ☐Unknown ☐ N/A

Estimated date of delivery mm_____/ dd_____/ yyyy_____

If N/A, date of termination (actual or planned) mm_____/ dd__/ yyyy_____

Has the pregnant female already delivered? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If yes, provide date of delivery: mm _____/ dd_____/ yyyy_____

Was the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If any Adverse Event was experienced by the infant, provide brief details:_____

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

FORM-115199 Version 1.0 Effective Date: 24-Sept-2018

Amgen Proprietary - Confidential

AMGEN® Lactation Notification Form

Report to Amgen at: USTO fax: +1-888-814-8653, Non-US fax: +44 (0)207-136-1046 or email (worldwide): svc-ags-in-us@amgen.com

1. Case Administrative Information

Protocol/Study Number: 20180060

Study Design: ☑ Interventional ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

2. Contact Information

Investigator Name _____ **Site #** _____

Phone (____)_____ **Fax** (____)_____ **Email** _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject age (at onset):** ____ (in years)

4. Amgen Product Exposure

Amgen Product	Dose at time of breast feeding	Frequency	Route	Start Date
				mm____/dd____/yyyy____

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm _____/dd_____/yyyy_____

Did the subject withdraw from the study? ☐ Yes ☐ No

5. Breast Feeding Information

Did the mother breastfeed or provide the infant with pumped breast milk while actively taking an Amgen product? ☐ Yes ☐ No

If No, provide stop date: mm_____/dd_____/yyyy_____

Infant date of birth: mm_____/dd_____/yyyy_____

Infant gender: ☐ Female ☐ Male

Is the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If any Adverse Event was experienced by the mother or the infant, provide brief details:_____

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

FORM-115201 Version 1.0 Effective Date: 24-Sept-2018

12.6 Appendix 6. Sample Storage and Destruction

Any blood (biomarker or pharmacogenetic) sample collected according to the Schedule of Activities (Table 2-1) can be analyzed for any of the tests outlined in the protocol and for any tests necessary to minimize risks to study subjects. This includes testing to ensure analytical methods produce reliable and valid data throughout the course of the study. This can also include, but is not limited to, investigation of unexpected results, incurred sample reanalysis, and analyses for method transfer and comparability.

All samples and associated results will be coded prior to being shipped from the site for analysis or storage. Samples will be tracked using a unique identifier that is assigned to the samples for the study. Results are stored in a secure database to ensure confidentiality.

If informed consent is provided by the subject, Amgen can do additional testing on remaining samples (ie, residual and back-up) to investigate and better understand migraines, the dose response and/or prediction of response to AMG 334, and characterize aspects of the molecule (eg, mechanism of action/target, metabolites). Results from this analysis are to be documented and maintained, but are not necessarily reported as part of this study. Samples can be retained for up to 20 years.

Since the evaluations are not expected to benefit the subject directly or to alter the treatment course, the results of pharmacogenetic, biomarker development or other exploratory studies are not placed in the subject's medical record and are not to be made available to the subject, members of the family, the personal physician, or other third parties, except as specified in the informed consent.

The subject retains the right to request that the sample material be destroyed by contacting the investigator. Following the request from the subject, the investigator is to provide the sponsor with the required study and subject number so that any remaining blood samples and any other components from the cells can be located and destroyed. Samples will be destroyed once all protocol-defined procedures are completed. However, information collected from samples prior to the request for destruction, will be retained by Amgen.

The sponsor is the exclusive owner of any data, discoveries, or derivative materials from the sample materials and is responsible for the destruction of the sample(s) at the request of the subject through the investigator, at the end of the storage period, or as appropriate (eg, the scientific rationale for experimentation with a certain sample type no

longer justifies keeping the sample). If a commercial product is developed from this research project, the sponsor owns the commercial product. The subject has no commercial rights to such product and has no commercial rights to the data, information, discoveries, or derivative materials gained or produced from the sample. See Section 12.3 for subject confidentiality.

12.7 Appendix 7. Hepatotoxicity Stopping Rules: Suggested Actions and Follow-up Assessments and Study Treatment Rechallenge Guidelines

Subjects with abnormal hepatic laboratory values (ie, alkaline phosphatase [ALP], aspartate aminotransferase [AST], alanine aminotransferase [ALT], total bilirubin [TBL]) and/or international normalized ratio (INR) and/or signs/symptoms of hepatitis (as described below) may meet the criteria for withholding or permanent discontinuation of Amgen IP or other protocol-required therapies, as specified in the *Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009*.

Criteria for Withholding and/or Permanent Discontinuation of Amgen Investigational Product and Other Protocol-required Therapies due to Potential Hepatotoxicity

The following stopping and/or withholding rules apply to subjects for whom another cause of their changes in liver biomarkers (TBL, INR and transaminases) has not been identified.

Important alternative causes for elevated AST/ALT and/or TBL values include, but are not limited to:

- hepatobiliary tract disease
- viral hepatitis (eg, hepatitis A/B/C/D/E, Epstein-Barr Virus, cytomegalovirus, herpes simplex virus, varicella, toxoplasmosis, and parvovirus)
- right-sided heart failure, hypotension or any cause of hypoxia to the liver causing ischemia
- exposure to hepatotoxic agents/drugs or hepatotoxins, including herbal and dietary supplements, plants and mushrooms
- heritable disorders causing impaired glucuronidation (eg, Gilbert's syndrome, Crigler-Najjar syndrome) and drugs that inhibit bilirubin glucuronidation (eg, indinavir, atazanavir)
- alpha-one antitrypsin deficiency
- alcoholic hepatitis
- autoimmune hepatitis
- Wilson's disease and hemochromatosis
- nonalcoholic fatty liver disease including steatohepatitis
- non-hepatic causes (eg, rhabdomyolysis, hemolysis)

If IP(s) is/are withheld, the subject is to be followed for possible drug induced liver injury (DILI) according to recommendations in the last section of this appendix.

Rechallenge may be considered if an alternative cause for impaired liver tests (ALT, AST, ALP) and/or elevated TBL, is discovered and the laboratory abnormalities resolve to normal or baseline (see next section in this appendix).

Table 12-2. Conditions for Withholding and/or Permanent Discontinuation of Amgen Investigational Product and Other Protocol-required Therapies due to Potential Hepatotoxicity

Analyte	Temporary Withholding	Permanent Discontinuation
TBL	> 3 x ULN at any time	> 2 x ULN
		OR
INR	--	> 1.5 x (for subjects not on anticoagulation therapy)
	OR	AND
AST/ALT	> 8 x ULN at any time > 5 x ULN but < 8 x ULN for ≥ 2 weeks > 5 x ULN but < 8 x ULN and unable to adhere to enhanced monitoring schedule > 3 x ULN with clinical signs or symptoms that are consistent with hepatitis (such as right upper quadrant pain/tenderness, fever, nausea, vomiting, and jaundice)	In the presence of no important alternative causes for elevated AST/ALT and/or TBL values > 3 x ULN (when baseline was < ULN)
	OR	
ALP	> 8 x ULN at any time	--

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; INR = international normalized ratio; TBL = total bilirubin; ULN = upper limit of normal

Criteria for Rechallenge of Amgen Investigational Product and Other Protocol-required Therapies After Potential Hepatotoxicity

The decision to rechallenge the subject is to be discussed and agreed upon unanimously by the subject, investigator, and Amgen.

If signs or symptoms recur with rechallenge, then Amgen IP and other protocol-required therapies, as appropriate is to be permanently discontinued. Subjects who clearly meet the criteria for permanent discontinuation (as described in Table 12-2) are never to be rechallenged.

Drug-induced Liver Injury (DILI) Reporting and Additional Assessments

Reporting

To facilitate appropriate monitoring for signals of DILI, cases of concurrent AST or ALT and TBL and/or INR elevation, according to the criteria specified in the above, require the following:

- The event is to be reported to Amgen as a serious adverse event within 24 hours of discovery or notification of the event (ie, before additional etiologic investigations have been concluded)
- The appropriate Case Report Form (CRF) (eg, Event CRF) that captures information necessary to facilitate the evaluation of treatment-emergent liver abnormalities is to be completed and sent to Amgen

Other events of hepatotoxicity and potential DILI are to be reported as serious adverse events if they meet the criteria for a serious adverse event defined in Section 12.4.

Additional Clinical Assessments and Observation

All subjects in whom IP(s) or protocol-required therapies is/are withheld (either permanently or conditionally) due to potential DILI as specified in Table 12-2 or who experience AST or ALT elevations $>$ 3 x upper limit of normal (ULN) or 2-fold increases above baseline values for subjects with elevated values before drug are to undergo a period of “close observation” until abnormalities return to normal or to the subject’s baseline levels.

Assessments that are to be performed during this period include:

- Repeat AST, ALT, ALP, total bilirubin (TBL), and INR within 24 hours
- In cases of TBL $>$ 2 x ULN or INR $>$ 1.5, retesting of liver tests, TBL, and INR is to be performed every 24 hours until laboratory abnormalities improve

Testing frequency of the above laboratory tests may decrease if the abnormalities stabilize or the IP(s) or protocol-required therapies has/have been discontinued AND the subject is asymptomatic.

Initiate investigation of alternative causes for elevated AST or ALT and/or elevated TBL. The following are to be considered depending on the clinical situation:

- complete blood count with differential to assess for eosinophilia
- serum total immunoglobulin (Ig)G, anti-nuclear antibody anti-smooth muscle antibody, and liver kidney microsomal antibody-1 to assess for autoimmune hepatitis
- serum acetaminophen (paracetamol) levels

- a more detailed history of:
  - prior and/or concurrent diseases or illness
  - exposure to environmental and/or industrial chemical agents
  - symptoms (if applicable) including right upper quadrant pain, hypersensitivity-type reactions, fatigue, nausea, vomiting and fever
  - prior and/or concurrent use of alcohol, recreational drugs and special diets
  - concomitant use of medications (including non-prescription medicines and herbal and dietary supplements), plants, and mushrooms
- viral serologies
- creatine phosphokinase, haptoglobin, lactate dehydrogenase and peripheral blood smear
- appropriate liver imaging if clinically indicated
- appropriate blood sampling for pharmacokinetic analysis if this has not already been collected
- hepatology consult (liver biopsy may be considered in consultation with a hepatologist)

Follow the subject and the laboratory tests (ALT, AST, TBL, INR) until all laboratory abnormalities return to baseline or normal or considered stable by the investigator. The "close observation period" is to continue for a minimum of 4 weeks after discontinuation of all IP(s) and protocol-required therapies.

The potential DILI event and additional information such as medical history, concomitant medications and laboratory results must be captured in the corresponding CRFs.

Amendment 3

Protocol Title: Effect of Erenumab-aooe on Disability and Work Productivity in Employed Subjects with Episodic Migraine Who Have Previously Failed 1 or More Migraine Preventative Treatments

Amgen Protocol Number (AMG 334/Erenumab) 20180060

Amendment Date: 31 August 2020

Rationale:

The following changes were made to the protocol, dated August 31st, 2020, due to the COVID-19 pandemic. The COVID-19 pandemic has disrupted all clinical trials from an operational standpoint. However more importantly, the disruptions of this pandemic and its suppression effects are likely impacting this Work Productivity trial endpoints. Because of these unexpected changes in the way we work, measures had to be taken to mitigate their impact and to maintain the scientific rigor of our study. Hence, we have aligned on these new requirements as part of our protocol.

- Added weekly COVID-19 impact assessments to the schedule of activities
- Modified Investigational Product dosing instructions to include COVID-19 impact mitigation strategies

Other changes include:

- Added additional rationale regarding the use of EM subject population
- Added clarification to additional ongoing approvals to erenumab product background
- Modification to inclusion criterion #105 to include job stability assessment
- Modification to inclusion criterion #106 and #111 to clarify lost productive time
- Modification to exclusion criterion #232 and #233 to clarify opioid and butalbital or analgesics taken for greater than or equal to 4 days rather than greater than 4 days for the month prior to screening
- Clarification of excluded treatments described within Table 7-2

- Clarified incorrect treatment rather than incorrect dose within Safety Analysis Set
- Updated Common Terminology Criteria for Adverse Events versioning
- Administration, typographical, and formatting changes were made throughout the protocol

Amendment 2

Protocol Title: Effect of Erenumab-aooe on Disability and Work Productivity in Employed Subjects With Episodic Migraine Who Have Previously Failed 1 or More Migraine Preventive Treatments

Amgen Protocol Number (Erenumab-aooe [AMG 334]) 20180060

Amendment Date: 09 March 2020

Rationale:

This protocol is being amended to address the following:

1) Study periods and procedures
    - Introduction of up to 1 rescreening attempt in instances where the condition leading to screen failure is considered to be transient and likely to improve/resolve
2) Eligibility requirements
    - Reduction from 80% to 75% as the minimal eDiary compliance threshold for this study is proposed
    - Non-essential exclusion requirements are proposed to be removed or edited. These include:
        - Removal of BMI restrictions
        - Removal of restrictions for lifetime use of any type of anti-CGRP product use
        - Reduction of the exclusionary period for opioid/barbiturate use in excess of 4 days per month to the last month prior to screening
3) Concomitant medication/device/procedure
    - Allowance of a second concomitant oral migraine preventive medication in instances where a second medication is required to treat a comorbid medical condition (eg, depression, hypertension)
    - Removal of prohibition on certain procedures that may affect subjects lifestyle choices (eg, biofeedback, relaxation techniques)
4) Sample size
    - Editorial adjustments made to allow for the study to be finalized at the time of last subject enrolled for the primary analysis irrespective of the number of Science37 subjects enrolled

Amendment 1

Protocol Title: Effect of Erenumab-aooe on Disability and Work Productivity in Employed Subjects With Episodic Migraine Who Have Previously Failed 1 or More Migraine Preventive Treatments

Amgen Protocol Number 20180060

Amendment Date: 14 June 2019

Rationale:

This protocol is being amended to:

- Clarify information surrounding:
  - Data collection in regards to the primary, secondary, and exploratory endpoints.
  - Eligibility criteria between Part 1 and Part 2
  - Medication that is prohibited versus medication that is allowed with circumstances
  - Definition of prior treatment and concomitant medication
  - Medical history will include a targeted neurological medical history
- Align with changes being made across the AMG 334 program, which include:
  - Add biomarker collection (optional central laboratory)
  - Removed the need for local laboratory collection in a phase 4 trial
- Make editorial and administrative changes for grammatical reasons as well as for internal consistency within the protocol